Nos. 2023-2074, -2075, -2191, -2192,
-2193, -2194, -2239, -2252, -2253, -2255

United States Court of Appeals for the Federal Circuit

CYTIVA BIOPROCESS R&D AB,

Appellant

v.

JSR CORP., JSR LIFE SCIENCES, LLC,

Cross-Appellants

Appeals from the United States Patent and Trademark Office, Patent Trial and Appeal Board in Nos. IPR2022-00036, -00041, -00042, -00043, -00044, -00045

BRIEF OF CROSS-APPELLANTS JSR CORP. AND JSR LIFE SCIENCES, LLC

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February 5, 2024

EXEMPLARY CLAIMS

Claims 1 and 4 of U.S. Patent No. 10,213,765

1. A chromatography matrix comprising:

a solid support; and

a ligand coupled to the solid support, the ligand comprising at least two polypeptides,

wherein the amino acid sequence of each polypeptide comprises at least 55 contiguous amino acids of a modified SEQ ID NO. 1, and

wherein the modified SEQ ID NO. 1 has an alanine (A) instead of glycine (G) at a position corresponding to position 29 of SEQ ID NO. 1.

4. The chromatography matrix of claim 1, wherein the ligand is capable of binding to the Fab part of an antibody.

Claims 1 and 4 of U.S. Patent No. 10,343,142

1. A process for isolating one or more target compound(s), the process comprising:

(a) contacting a first liquid with a chromatography matrix, the first liquid comprising the target compound(s) and the chromatography matrix comprising:

(i) a solid support; and

(ii) at least one ligand coupled to the solid support, the ligand comprising at least two polypeptides, wherein the amino acid sequence of each polypeptide comprises at least 55 contiguous amino acids of a modified SEQ ID NO. 1, and wherein the modified SEQ ID NO. 1 has an alanine (A) instead of glycine (G) at a position corresponding to position 29 of SEQ ID NO. 1; and

(b) adsorbing the target compound(s) to the ligand; and,

(c) eluting the compound(s) by passing a second liquid through the chromatography matrix that releases the compound(s) from the ligand.

4. The process of claim 1, wherein the ligand binds to the Fab part of an antibody.

AMENDED CERTIFICATE OF INTEREST

Counsel for Cross-Appellants JSR Corp. and JSR Life Sciences, LLC certify the following:

1. Full name of party represented by me	2. Name of real party in interest represented by me	3. Parent corporations and publicly held companies that own 10% or more of stock in the party
JSR Corp.	None.	None.
JSR Life Sciences, LLC	None.	JSR Corp.

4. The names of all law firms and the partners or associates that appeared for the party now represented by me in the agency or are expected to appear in this court (and who have not or will not enter an appearance in this case) are:

None.

5. The title and number of any case known to counsel to be pending in this or any other court or agency that will directly affect or be directly affected by this court's decision in the pending appeal. *See* Fed. Cir. R. 47.5(a)-(b)

See Dkt. No. 8

6. Information required by Federal Rule of Appellate Procedure 26.1(b) and (c) that identifies organizational victims in criminal cases and debtors and trustees in bankruptcy cases.

Not Applicable

Dated: February 5, 2024

/s/ Eric W. Dittmann
Eric W. Dittmann

Counsel for Cross-Appellants JSR Corp. and JSR Life Sciences, LLC

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STATEMENT OF RELATED CASES

Cytiva filed suit in the United States District Court for the District of Delaware for alleged patent infringement of the claims challenged in *inter partes* reviews on appeal. *Cytiva BioProcess R&D et al. v. JSR Corp. et al.*, C.A. No. 21-310-RGA (D. Del.). That case has been stayed pending the final outcome of these IPRs.

INTRODUCTION

Cytiva's challenge to the unpatentability rulings of the Patent Trial and Appeal Board ("Board") lacks force. The patent claims at issue are directed to well-known features of chromatography matrices that use ligands to isolate and purify antibodies for therapeutic use. Naturally occurring Staphylococcal Protein A ("SPA") is frequently used for constructing ligands, and is composed of five highly homologous domains. It has been known for decades that a particular "G29A" mutation, traditionally applied to SPA Domain "B," improves the stability of the ligand. The only putatively novel feature of Cytiva's chromatography matrix patent claims is that the G29A substitution is made to Domain "C," one of the five highly homologous domains of SPA, instead of Domain B. This mutation (referred to herein as "C(G29A)"), however, was expressly taught in the prior art, and the Board properly found Cytiva's independent claims obvious as a result.

Cytiva attempts to circumvent the clear obviousness of its claims by a legal sleight-of-hand: It suggests a rigid, mandatory rule for any claim involving an allegedly new chemical compound that obviousness can be proven *only* through this Court's "lead compound" test typically applied in pharmaceutical cases. This Court has expressly disavowed such a rigid rule. It instead applies a lead-compound analysis when *a party asserts* obviousness in modifying a particular prior art lead compound to ensure that the challenger's choice is reasoned and supported by

evidence. The lead-compound construct ill-fits the chromatography apparatus and method claims at issue here, which involve an alteration to a naturally occurring protein specifically disclosed in the prior art. In fact, multiple prior art references disclose the exact claimed alteration *in a single paragraph*. But even if the lead-compound doctrine were deemed to apply, JSR amply demonstrated that Domain C would have been an ideal starting point for modification. Indeed, Cytiva itself used Domain C in its prior art commercial product—MabSelect™—negating its litigation-inspired arguments that a person of ordinary skill in the art ("POSA") would not have thought to start with Domain C.

Cytiva's attempt to rescue its dependent apparatus claims—which add a limitation that the ligand is "capable of binding to the Fab part of an antibody"—fares no better. Cytiva has conceded that Fab binding is an inherent property of the claimed chromatography matrix. Claim limitations reciting merely inherent properties lack patentable weight, and this Court has held that, where the combination would have been obvious for reasons independent of the inherent feature (as here), the challenger need not prove that a POSA would have reasonably expected success in achieving a property inherent in the combination. An obvious combination does not become nonobvious regardless of whether an inherent property is known or reasonably predicted in advance (which is in any event the case here). Cytiva cannot distinguish the precedents cited by the Board in rejecting its

arguments. Instead, Cytiva attempts to weave a contrary rule from out-of-context snippets that address an entirely inapposite issue (namely, that an unknown, unexpected property cannot supply motivation to combine). This Court should uphold all of the Board's unpatentability rulings.

The Board did err in its disposition of four dependent "Fab binding" method claims, which are the subject of JSR's cross-appeal. The Board misinterpreted the plain claim language as limited to isolation of Fab fragments—the claims are broader, and encompass a process of isolating a "target compound" using the chromatography ligand, wherein the ligand "binds to the Fab part of an antibody," and not just isolating fragments of an antibody. This includes binding to the Fab portion of a whole Immunoglobulin G ("IgG") antibody in the process of isolating IgG as a target compound. Under the proper claim construction, the Fab binding method claims merely recite a result that would have been inherent in the process of the independent claims that were found obvious. This alone warrants reversal. But even under the Board's construction, its ruling on the dependent method claims was erroneous because the Board (i) did not address one of JSR's obviousness theories and (ii) required a level of Fab binding not supported by the claims.

ISSUES PRESENTED

1. Whether the Board correctly rejected Cytiva's proposed rigid application of a lead-compound analysis to JSR's straightforward obviousness combination in which the prior art taught directly the single claimed G29A modification to any of the naturally occurring SPA domains, including Domain C.

2. Whether the Board correctly determined that the inherent Fab binding property of the obvious C(G29A) ligand does not add patentable weight to the claims under either a reasonable expectation of success or secondary considerations framework.

3. Whether the Board erred in: (i) requiring JSR to demonstrate a reasonable expectation of success in isolating Fab fragments, which is not required by any claim; (ii) overlooking the obviousness of the Fab binding method claims based on a combination ligand, as taught by the prior art; and (iii) finding no reasonable expectation of success in at least minimal Fab binding by the obvious C(G29A) ligand.

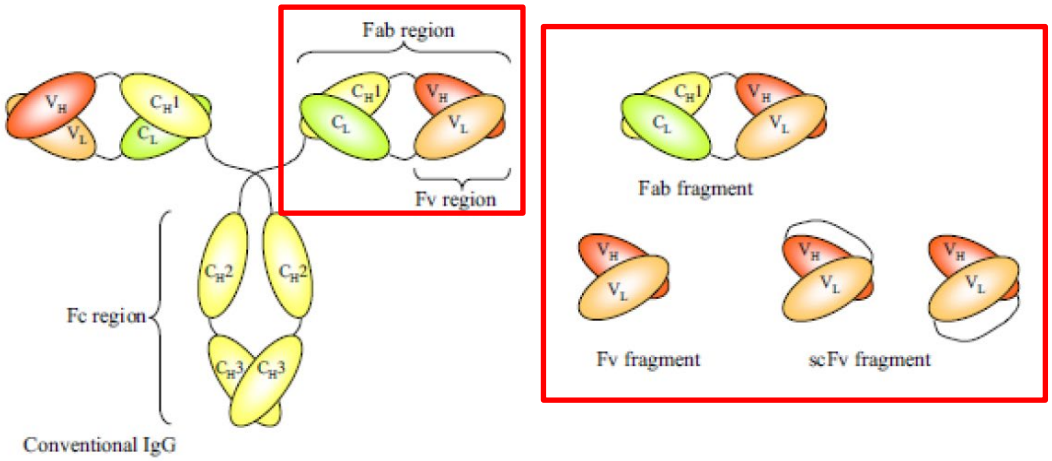
STATEMENT OF THE CASE

I. STAPHYLOCOCCAL PROTEIN A CHROMATOGRAPHY

A. Chromatographic Antibody Purification

Antibodies, also called immunoglobulins, are glycoproteins that recognize foreign molecules called antigens. Appx5801. The IgG class of antibodies is

composed of an "Fc region" and a "Fab region," the latter of which can be broken down into "Fab fragments" when the whole antibody is digested by an enzyme. Appx5802-5803; Appx2965. Antigens can bind to either a whole antibody or a fragment of an antibody. Appx5802-5803. As illustrated in the background of the decisions at issue, the Board recognized the difference between the "Fab region" of IgG and "Fab fragments":

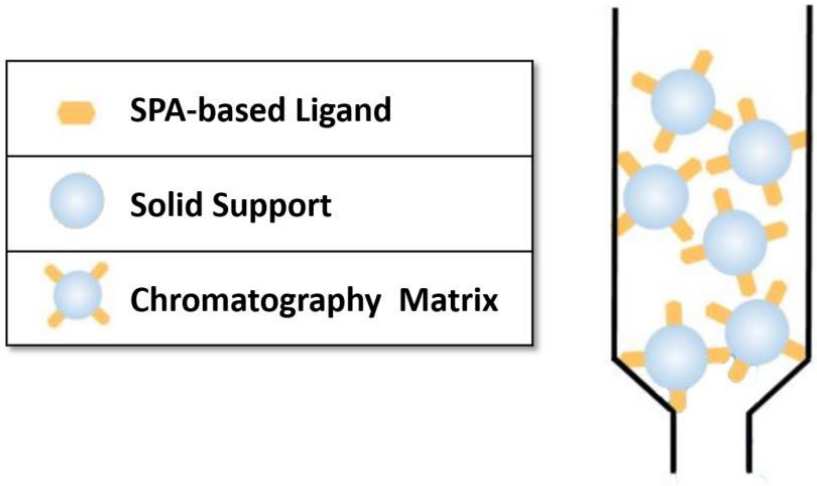


Appx5802 (Figure 1) (annotations added); Appx60 (reproducing this figure).

Because antibodies are essential to many therapeutic treatments, methods of isolating and purifying antibodies have been used for decades. Appx2964. Isolation and purification methods often rely on ligands—polypeptides that can selectively bind to specific targets—to isolate the antibodies of interest. Appx2965-2966. Ligands can be single protein "monomers" or a multimeric protein called a "multimer." Appx2973-2974; Appx2982-2983; Appx3850.

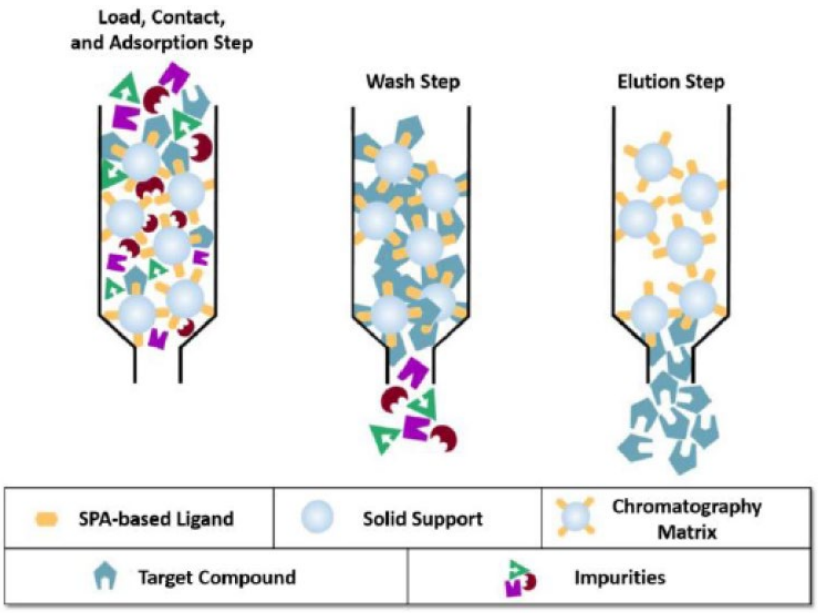
In an affinity chromatography matrix—a device commonly used for isolating

antibodies—an antibody-binding ligand is attached to a solid support packed into a chromatography column. Appx2967-2970.



Appx2966.

To isolate antibodies, a fluid containing the target antibody is loaded into the column. Appx2970-2971. Due to the ligand's selective binding, the impurities flow through the column or are removed in a subsequent washing step, whereas the ligand binds the antibodies. Appx2970-2971; Appx3855. Finally, a solution is applied to the column to release or "elute" the ligand-bound antibodies. Appx2970-2971; Appx3855. These well-known chromatography steps are not at issue in this appeal.



Appx2970-2971.

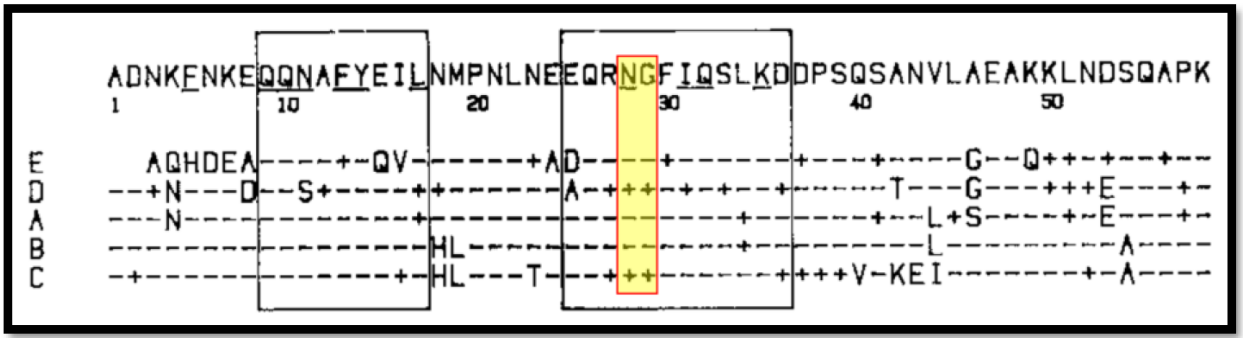
After completion of the process, contaminants must be removed before the column can be reused, which is valuable from a cost perspective. This procedure, which typically entails running an alkaline solution over the column, is called cleaning-in-place ("CIP"). Appx2971-2972; Appx3840.

B. Staphylococcal Protein A

SPA is a constituent of the cell wall of the bacterium *Staphylococcus aureus*, which can cause serious infections in humans. Appx2964. SPA is partly responsible for the bacterium's virulence because SPA binds well to IgG, which is released by the immune system to fight infection. *Id.* This binding prevents the IgG from attacking the bacteria. *Id.* SPA has long been used in affinity chromatography matrices due to this well-known IgG binding. Appx2965-2966; Appx2973-2974; Appx371. SPA is composed of five highly homologous domains, "E," "D," "A,"

"B," and "C." Appx2966-2967; Appx3905-3906. Each of the five natural domains binds both the Fc and Fab portions of antibodies. Appx2965-2966; Appx3815; Appx7373-7375.

SPA-based ligands can be either naturally occurring or synthetic, where the amino acid sequence has been mutated. Appx2967-2968. Because CIP involves high-alkaline conditions, which can degrade proteins, increased ligand stability in alkaline environments is desirable. Appx2972-2973; Appx371; Appx3840-3841. It has long been known that asparagine-glycine linkages (N-G), found at positions 28 and 29 of each of the five SPA domains, are particularly weak in alkaline conditions.



Appx2972-2973 (annotating Appx3906).

Substituting the glycine at position 29 for alanine, also called a "G29A" modification, has been known since the 1980s to promote alkaline stability by avoiding this problematic asparagine-glycine connection. Appx2974-2977; Appx3901; Appx3816. Applying this G29A modification to the B domain yielded the widely used, synthetic "Z" domain. Appx2973-2978; Appx3898. Cytiva's claimed invention merely applies the same well-known, straightforward method of

improving alkaline stability, the G29A modification, to one of the other four naturally occurring SPA homologs—which, as explained below, the prior art expressly taught.

II. CYTIVA'S PATENT CLAIMS

U.S. Patent Nos. 10,213,765 ("the '765 patent"), 10,323,142 ("the '142 patent"), and 10,875,007 ("the '007 patent") relate to SPA ligand-based chromatography matrices. The '765 patent describes a C(G29A) chromatography matrix. Appx2978-2979. Claims 1 and 4 of the '765 patent are representative:

> 1. A chromatography matrix comprising:
> a solid support; and
> a ligand coupled to the solid support, the ligand comprising at least two polypeptides,
> wherein the amino acid sequence of each polypeptide comprises at least 55 contiguous amino acids of a modified SEQ ID NO. 1, and
> wherein the modified SEQ ID NO. 1 has an alanine (A) instead of glycine (G) at a position corresponding to position 29 of SEQ ID NO. 1.
>
> 4. The chromatography matrix of claim 1, wherein the ligand is capable of binding to the Fab part of an antibody.

Appx378. "SEQ ID NO. 1" is the C domain, so the claim requires a ligand containing C(G29A). Appx2979-2981.

The '142 and '007 patents describe a process for using this chromatography matrix to isolate target compounds. Appx3112-3114. Claims 1 and 4 of the '142 patent are representative:

1. A process for isolating one or more target compound(s), the process comprising:
(a) contacting a first liquid with a chromatography matrix, the first liquid comprising the target compound(s) and the chromatography matrix comprising:
(i) a solid support; and
(ii) at least one ligand coupled to the solid support, the ligand comprising at least two polypeptides, wherein the amino acid sequence of each polypeptide comprises at least 55 contiguous amino acids of a modified SEQ ID NO. 1, and wherein the modified SEQ ID NO. 1 has an alanine (A) instead of glycine (G) at a position corresponding to position 29 of SEQ ID NO. 1; and
(b) adsorbing the target compound(s) to the ligand; and
(c) eluting the compound(s) by passing a second liquid through the chromatography matrix that releases the compound(s) from the ligand.

4. The process of claim 1, wherein the ligand binds to the Fab part of an antibody.

Appx391.

None of the claims in Cytiva's asserted patents specifically recites Fab *fragment* isolation. Instead, the dependent claims require isolation of a "target compound" in which "the ligand binds to the Fab part of an antibody." *Id.* The claims do not restrict the target compound to Fab fragments.

III. THE PRIOR ART

A. Abrahmsén

Abrahmsén[1] teaches incorporating a G29A mutation to improve SPA-domain stability for use in antibody binding. Appx3833; Appx2991-2994. Abrahmsén does not limit this principle to a specific domain: "According to still another aspect of

[1] U.S. Patent No. 5,143,844. Appx3825-3838.

the invention[,] there is provided for a recombinant DNA fragment coding for ***any of*** the E D A B ***C*** domains of staphylococcal protein A, wherein the ***glycine codon(s) in the Asn-Gly coding constellation has been replaced by an alanine codon***." Appx3833 (2:32-37)[2]; Appx2993.

Although Abrahmsén arises in the context of a fusion-protein strategy[3] to purify antibodies, it was widely accepted by 2006 as providing relevant teachings regarding construction of SPA-based chromatography matrices. Appx2994; Appx3816; Appx3849; *see also* Appx5009 (Cytiva asserting that the Abrahmsén patent covers its MabSelect SuRe™ Ligand, which is a Domain Z-based chromatography ligand).

B. Linhult

Linhult[4] describes SPA-based chromatography and strategies for increasing the stability of SPA-based ligands in CIP-associated alkaline conditions. Appx2983-2991; Appx3815-3816. Linhult confirms that all five highly homologous, naturally occurring SPA domains, including Domain C, possess high affinity and selectivity

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[2] All emphasis added unless specified otherwise.

[3] In this technique, a fused SPA and target protein are purified in an IgG-based affinity column and the target protein is detached from the SPA and isolated. Appx17; Appx4900-4902.

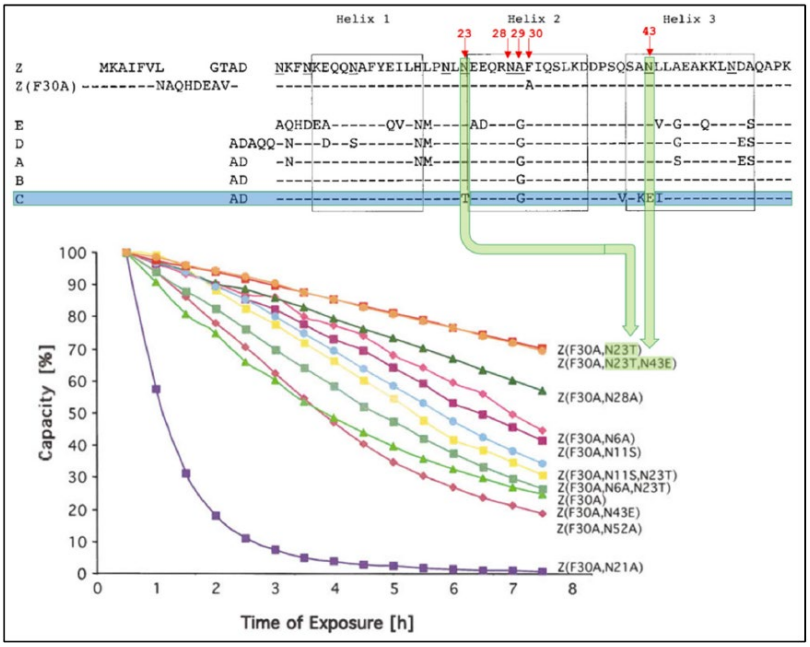
[4] Linhult, *et al.*, "Improving the Tolerance of a Protein A Analogue to Repeated Exposures Using a Bypass Mutagenesis Approach," PROTEINS: Structure, Function, and Bioinf., 55:407-16 (2004) ("Linhult") (Online Version). Appx3815-3824.

for antibodies. Appx2984-2985; Appx3815. Linhult further describes how characteristics such as "high tolerance to both low pH and high pH" treatments have made SPA-based chromatography matrices "probably … the most widely used medium for isolation of monoclonal antibodies and their fragments." Appx3815.

Though SPA-based chromatography matrices were already considered "relatively stable" under alkaline conditions at the time, Linhult makes clear that it was still desirable to "***further*** improve [SPA's] stability in order to enable an SPA-based affinity medium to withstand even longer exposure to the harsh conditions associated with CIP." Appx3816; Appx2985. Linhult specifically identifies the asparagine-glycine linkage present in all five SPA domains as "the most sensitive amino acid sequence to alkaline conditions," and references demonstrated success in making a G29A mutation "to avoid the amino acid combination asparagine-glycine." Appx3816; Appx2985.

Linhult also discloses experiments analyzing the stability of certain Z domain-based ligands in alkaline conditions. Appx3818-3819; Appx2986-2989. Linhult makes specific residue substitutions to the Z domain based other homologous SPA domains—for example, one of the best-performing ligands contained threonine ("T") and glutamic acid ("E") substitutions at positions 23 and 43, respectively. Appx3818-3819; Appx2988. T and E occur naturally at these positions *only* in SPA's C domain. Appx3816 (Fig. 1(A)); Appx2987. Linhult also emphasized that

this reliance on homologous structures (such as the C domain, which is reflected in the annotated figure below), was an "obvious" decision. Appx3817; Appx2989.



Appx3816 (Fig. 1(a)); Appx3819 (Fig. 2); Appx2989.

Linhult also demonstrates that the Domain C-inspired Z(N23T) ligand outperformed Z-based ligands in resisting alkaline conditions. Appx2990-2991.

C. Hober

Hober[5] discloses SPA-based chromatography matrices and conventional techniques for constructing these matrices. Appx3851-3854; Appx2994-3001. Hober also discloses that the G29A mutation is "advantageous for structural stability

[5] International Patent Application Publication No. WO 03/080655. Appx3839-3895.

reasons," and can be performed on any of the five SPA domains. Appx3851; Appx2997-2998; Appx3025. Specifically:

> In a specific embodiment, the present multimer also comprises ***one or more of the E, D, A, B, and C domains*** of Staphylococcal protein A. In this embodiment, it is preferred that asparagine residues located in loop regions have been mutated to more hydrolysis-stable amino acids. In an embodiment advantageous for structural stability reasons, the ***glycine residue in position 29 of SEQ ID NOS. 1 has also been mutated, preferably to an alanine residue***.

Appx3851; Appx3024-3025.

Hober provides data from an alkaline stability study analyzing certain SPA ligands that incorporate the C domain-specific N23T mutation. Appx3875-3877; Appx2998-3000. Hober, like Linhult, also reported greater alkaline stability of Z(N23T)-based ligands in a head-to-head comparison with Z-based ligands. Appx3000-3001.

Hober also expressly teaches a combination multimer ligand. Specifically, Hober teaches that "another aspect of the present invention is a multimer comprised of at least one of the mutated proteins according to the invention together with one or more further units." Appx3850; Appx3851 ("[T]he present multimer also comprises one or more of the E, D, A, B, and C domains of [SPA].").

D. Berg[6]

Berg is directed to the structure of a chromatography matrix used to isolate antibodies. Appx4164; Appx3464-3466. Berg suggests using ligands made up of one or more domains A, B, C, D, and E, with a preference for "Domain B and/or Domain C." Appx4166.

IV. PROCEEDINGS BELOW

Cytiva brought suit in the United States District Court for the District of Delaware alleging that JSR infringed the three patents at issue. *Cytiva BioProcess R&D et al. v. JSR Corp. et al.*, C.A. No. 21-310-RGA (D. Del. Feb. 26, 2021). JSR filed petitions for *inter partes* review challenging all 83 claims asserted in the district court. Appx406-863. JSR relied on Linhult and Berg as principal references in the underlying IPRs, combining them with Abrahmsén and Hober, and filed two IPRs for each patent, one per primary reference. *Id.*; Appx2946-3077; Appx3078-3243; Appx5526-5561; Appx5490-5525. The Board granted institution as to all six petitions, Appx1073-1158; Appx1171-1349, and issued three final written decisions, one for each patent, Appx1-352. For the purposes of this brief, JSR uses IPR2022-00036 as representative of the matrix apparatus claims and IPR2022-00041 as

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[6] U.S. Patent Application Publication 2006/0134805. Appx4162-4171. This reference was not considered on the merits by the Board for the independent claims. Appx51 (not reaching Berg grounds for matrix claims); Appx109-111 (addressing Berg only in the context of Fab-binding dependent method claims).

representative of the method claims.

The Board, in its final written decisions, ultimately found all challenged claims unpatentable except for the dependent Fab-binding method claims—claims 4 and 17 of the '142 patent and claims 11 and 29 of the '007 patent. Appx1-352. As to the independent claims of all three patents, the Board agreed with JSR that the prior art taught making the G29A mutation in *any one* of the SPA-binding domains, including Domain C, and found that JSR had proven both a sufficient motivation for making the combination and a reasonable expectation of success in doing so. Appx35; Appx44; Appx101. The Board also rejected Cytiva's argument that JSR failed to identify a reason to select Domain C, basing its decision on the express teachings of the prior art to make the G29A modification to any one of the five SPA domains. Appx35-38; Appx91-93.

The Board also agreed that, with respect to the Fab binding matrix claims 4 and 17 of the '765 patent, "[t]he prior art does not need to recognize that Domain C retains the ability to bind Fab fragments after a G29A mutation," given JSR's articulated rationale of improved alkaline stability. Appx48. This was because the "capable of binding" language of those dependent claims did not "add any structural limitations to claim 1[;] it merely recites the function of the composition when used for example in an assay." Appx46. In such circumstances, the Board found properties inherent in the structure claimed in the independent claims do not render

patentable dependent claims directed to the property. *Id.*

The Board drew a distinction, however, as to the Fab binding method claims. For those claims, the Board found a lack of reasonable expectation of success in isolating Fab fragments as the target compounds, Appx101-105 & n.12; Appx277-281 & n.12, even though the claims do not require Fab fragments to be the target compound or that the ligand binds to a Fab fragment. The Board based its decision on its understanding of a single figure in the "Jansson" reference (Figure 3) as showing "the loss of Fab binding," Appx103-104; Appx279-280, even though Jansson shows only a reduction in Fab binding, not its elimination.

The Board did not resolve the parties' dispute regarding: (i) JSR's alternative unpatentability rationale based on a combination ligand or (ii) the level of Fab binding required to meet the claims.

SUMMARY OF ARGUMENT

Appeal

1. This Court should uphold the Board's unpatentability rulings with respect to the independent claims. As the Board ruled, the prior art expressly taught that the G29A modification can be applied to any of the SPA domains, including Domain C, for the express purpose of avoiding protein degradation in highly alkaline environments, and it would have been obvious to combine the prior-art teachings to achieve the claimed invention.

Cytiva's only argument on appeal is to fault the Board for not employing the two-part lead-compound test of this Court's precedents. That test requires that a POSA would have selected the asserted prior-art compounds out of many alternatives as lead compounds for modification, and that the prior art would have supplied the POSA with a motivation to arrive at the claimed compound with a reasonable expectation of success. But this Court has disclaimed the lead-compound test as mandatory simply because a claim contains limitations involving potentially novel chemical structures, holding that it applies only to obviousness challenges predicated on sifting through the prior art to identify a compound that would then be optimized by a POSA. The decision to implement a known modification in homologous, natural domains of ***the same protein*** (*i.e.*, SPA), in which the modification has previously been made, does not require identification of prior-art

compounds. As the Supreme Court has broadly taught, where there is a design need and a finite set of identified, predictable solutions, that alone provides a POSA "good reason to pursue the known options within his or her technical grasp." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007).

Even if the lead-compound rule were deemed a universal, mandatory rule that applies here, JSR amply satisfied that test. Contrary to Cytiva's intimations, it is perfectly permissible to have multiple lead compounds. As the Board found, the prior art specifically identified each of the five natural domains of SPA as candidates for the G29A modification, and taught that each of the five domains had strong affinity attributes and widespread use in affinity ligands for antibody purification. Given Linhult's and Hober's teachings of a G29A-containing SPA ligand attached to a chromatography matrix, this would have motivated a POSA to start with any one of the five SPA domains. Moreover, while there may be some general unpredictability in the field, Abrahmsén's computer modeling predicted success in making the specific C(G29A) mutation without negatively affecting antibody-binding capabilities, as the Board properly found. Furthermore, Domain C itself stood out as a lead compound given that the modifications tested in Linhult were based on Domain C, and the prior art specifically pointed to the promise of that domain (including the highest level of Fab binding among the natural domains). Even Cytiva itself used Domain C in a prior-art commercial product.

2. Cytiva's challenge to the Board's ruling on the dependent matrix claims likewise fails. Those dependent claims merely recite an inherent property of the chromatography matrix of the independent claims: namely, that the ligand is capable of binding to the Fab part of the antibody. Claim limitations that recite the inherent properties of an otherwise obvious composition have no patentable weight. Accordingly, this Court has held that, if a composition is obvious, the recitation of an inherent property thereof does not render it nonobvious, and it is unnecessary to inquire whether a POSA would have reasonably expected success in achieving the inherent property.

Cytiva cannot distinguish the Board's cited precedents, and instead attempts to fashion its own rule by plucking out-of-context statements from inapposite cases addressing the motivation requirement. Its novel proposed rule—that a reasonable expectation of success in achieving an inherent property must be shown except where "the patentee's claims drawn to the inherent features of that formulation add little or no value for the public," Cytiva Br. ("CB") 57, is foreclosed by precedent, unworkable, and unfounded.

Cross-Appeal

3. The Board erred in determining that JSR had not shown the Fab binding method claims to be unpatentable. The Board based its determination on a perceived lack of reasonable expectation of success, but the demanded success is not a feature recited by the claims. The Board misunderstood the Fab binding method claims to require isolation of Fab fragments, but the claims cover isolating any "target compounds," which can be whole antibodies, and are not limited to Fab fragments. And the claims simply recite that the "ligand binds to the Fab ***part of an antibody***," not merely Fab fragments separated from the rest of the antibody.

Thus, the Fab binding method claims fail for the same reason as the matrix claims—they merely recite an inherent feature in the obvious process of the independent claims. The Board determined that the independent claims reciting isolation of a target compound with a C(G29A)-based matrix was rendered obvious by a combination of Linhult, Abrahmsén, and/or Hober in which the G29A modification was made to the C domain and the ligand was used to purify whole IgG. Whole IgG indisputably contains a "Fab part," and Cytiva concedes that C(G29A) inherently possesses Fab-binding ability. That means that Fab binding inherently occurs to the Fab part of whole IgG when performing the isolation process that was determined to be obvious for the independent claims. As such, the Fab

binding method claims are unpatentable because they merely recite a result that inherently would occur during the performance of an otherwise obvious process.

4. Even if the dependent method claims required isolation of Fab fragments, the claims would have been obvious. Hober expressly suggests creating ligands with multiple, different monomers. JSR argued that a POSA would have had a separate motivation to isolate Fab fragments, in addition to alkali-stability, and that such a POSA would have been instructed by the prior art to combine a desired monomer ligand with any one of the natural SPA domains, which were known to bind Fab. The Board made no determinations as to this alternative unpatentability rationale. Due to the imbalance in the record evidence, the Court can reverse, but at a minimum should remand for the Board to determine this issue in the first instance.

5. Finally, the Board erred in finding no reasonable expectation of success in achieving Fab binding with a C(G29A) ligand. The prior art and Cytiva's own expert evidenced the C domain's superior ability to bind Fab as compared to all other natural SPA domains, showing it would be expected to retain some level of Fab binding when modified with a G29A mutation—even though the precise level of binding required is indeterminate, as demonstrated by Cytiva's repeatedly shifting positions. Cytiva introduced evidence that tended to show that Fab binding decreased when the G29A modification was made to the B domain, but the evidence was mixed and, at best, showed a reduction—not elimination—of Fab-binding

ability. As such, the Board's finding that the prior art showed a complete "loss" of Fab binding was not supported by substantial evidence. And because the claims require only a minimal amount of Fab binding, a POSA would have reasonably expected success in achieving this minimal threshold with the most-promising-for-Fab-binding Domain C, even with a G29A modification that might reduce binding to some degree.

ARGUMENT

I. STANDARD OF REVIEW

This Court reviews the Board's findings of fact for substantial evidence. *Univ. of Strathclyde v. Clear-Vu Lighting LLC*, 17 F.4th 155, 160 (Fed. Cir. 2021). Substantial evidence "means such relevant evidence as a reasonable mind might accept as adequate to support a conclusion." *In re Gartside*, 203 F.3d 1305, 1312 (Fed. Cir. 2000) (citations omitted). This Court reviews the Board's legal conclusions de novo. *Strathclyde*, 17 F.4th at 160.

"The Board's claim constructions … are determinations of law reviewed de novo where based on intrinsic evidence, with any Board findings about facts extrinsic to the patent record reviewed for substantial-evidence support." *St. Jude Med., LLC v. Snyders Heart Valve LLC*, 977 F.3d 1232, 1238 (Fed. Cir. 2020). In construing claim terms, the Board should take into account the patent's lexicography. *CCS Fitness, Inc. v. Brunswick Corp.*, 288 F.3d 1359, 1366 (Fed. Cir.

2002).

Obviousness is a question of law based on underlying findings of fact. *Strathclyde*, 17 F.4th at 160. The failure to evaluate claim scope properly in an obviousness determination is a legal question reviewed de novo. *Allergan, Inc. v. Apotex Inc.*, 754 F.3d 952, 966 (Fed. Cir. 2014).

II. THE BOARD DID NOT ERR IN DECLARING THE INDEPENDENT CLAIMS UNPATENTABLE

With regard to the independent claims, Cytiva's principal argument is that the Board erred in not performing a lead-compound analysis as a threshold step in assessing obviousness. CB 22-43. But the Board correctly determined that such a lead-compound analysis was not warranted because the prior art "expressly suggest[ed]" making the claimed modification to "any one" of the five natural SPA domains, including Domain C. Appx34; Appx37-38; *see also* Appx1198-1200. With such an express prior-art teaching, "making the G29A mutation in ***any one*** of the domains would have been obvious." Appx37-38. This properly reflects the "expansive and flexible approach" to obviousness described in *KSR*, 550 U.S. at 415-16, whereas Cytiva invites this Court to define rigid obviousness rules of the kind the Supreme Court disavowed in *KSR*. The lead-compound analysis that Cytiva demands is inapplicable to the apparatus and method claims at issue in view of the prior art disclosures and the nature of JSR's obviousness arguments. But even if a lead-compound analysis were required, the five native SPA domains would each be

lead compounds, with Domain C being among a discrete number of preferred starting points.

A. The Prior Art Directly Suggested the Combination of the Independent Claims

Cytiva's independent claims require only a single G29A modification to the well-known, naturally occurring Domain C. No other limitations of the independent claims—all of which recite commonplace chromatography components and methods known in the prior art—were contested below or on appeal. *See* Appx1787 n.1. And chromatography for antibody purification using SPA-based ligands and high-alkaline CIP processes was not new. *See supra* at 4-9. Furthermore, the five natural SPA domains were well-documented as "highly homologous." Appx31. Cytiva contests none of this on appeal.

As to the key claim limitation, the prior art taught that the G29A modification was desirable to increase the alkaline stability of the ligand, a fact Cytiva has never contested. Appx34-35; Appx90. Both Abrahmsén and Hober then explicitly taught—within a single paragraph in each reference—making this very modification to any one of the SPA domains, specifically calling out each of the five E, D, A, B, and C domains:

> According to still another aspect of the invention there is provided for a recombinant DNA fragment coding for any of the E D A B C domains of staphylococcal protein A, wherein the glycine codon(s) in the Asn-Gly coding constellation has been replaced by an alanine codon.

Appx3833 (2:32-37);

> In a specific embodiment, the present multimer also comprises one or more of the E, D, A, B, and C domains of Staphylococcal protein A. In this embodiment, it is preferred that asparagine residues located in loop regions have been mutated to more hydrolysis-stable amino acids. In an embodiment advantageous for structural stability reasons, the glycine residue in position 29 of SEQ ID NOS. 1 has also been mutated, preferably to an alanine residue. Also, it is

Appx3851; Appx2997-2998.

B. The Lead-Compound Analysis Is Inapplicable

Although Cytiva identifies safeguarding against hindsight bias as the lead-compound test's purpose, CB 25-26, such bias is not present here. The prior art expressly taught the precise modification necessary (G29A) to the individual domain in question (Domain C), provided a reason for that modification (alkaline stability), and showed that it would not impact a POSA's objectives in achieving the claim limitations (binding IgG). In such circumstances, the lead compound analysis is unwarranted, as the Board correctly determined. Appx91-93; Appx1200.

Cytiva mischaracterizes the lead-compound analysis as mandatory in any case involving chemical compositions. One of the leading precedents explaining the doctrine, *Otsuka Pharmaceutical Co. v. Sandoz, Inc.*, 678 F.3d 1280 (Fed. Cir. 2012), states the contrary. There, the Court applied the lead-compound test because "[i]n this case … the parties' arguments focus on selecting and modifying particular prior art compounds, designated as lead compounds." *Id.* at 1291 (identifying example of "[n]ew compounds … created from theoretical considerations rather than from attempts to improve on prior art compounds" as not triggering test); *see also Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1357 & n.3 (Fed. Cir. 2007) ("Alphapharm's obviousness argument rested entirely on the court making a preliminary finding that the prior art would have led to the selection of compound b as the lead compound, and Alphapharm failed to prove that assertion[.]").

When a compound's alleged obviousness is based on optimization of prior-art compounds—as opposed to, as here, an apparatus using a naturally occurring protein domain modified with a particular genetic substitution expressly associated with that same protein domain—the determination involves first "determin[ing] whether a chemist of ordinary skill would have selected the ***asserted prior art compounds*** as lead compounds, or starting points, for further development efforts." *Otsuka,* 678 F.3d at 1291. This portion of the Court's "analysis focuses ***on those proposed lead***

compounds that the alleged infringer has attempted to prove … that the skilled artisan would have had a reason to select from the panoply of known compounds in the prior art." *Id.* at 1292. Second, the Court analyzes whether "the prior art would have supplied one of ordinary skill in the art with a reason or motivation to modify a lead compound to make the claimed compound with a reasonable expectation of success." *Id.*

The lead-compound analysis fully comports with *KSR* when applied to obviousness contentions based on optimizing prior-art compounds. As this Court has explained, *KSR*: (1) "assumes a starting reference point or points in the art, prior to the time of invention, from which a skilled artisan might identify a problem and pursue potential solutions"; (2) "presupposes that" there must be "reasons" to modify the prior art; and (3) presumes "reasons for narrowing the prior art universe to a 'finite number of identified, predictable solutions.'" *Eisai Co. Ltd. v. Dr. Reddy's Lab'ys, Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008) (quoting *KSR*, 550 U.S. at 402). The purpose of the lead-compound analysis is to ensure "the reasoned identification of a lead compound," rather than allow "unsupported assertion[s regarding] compounds [that] might have served as lead compounds." *Id.*

Otsuka illustrates the benefit of the lead-compound analysis in winnowing unsubstantiated claims that a POSA would have chosen a particular lead compound from the "panoply of known compounds in the prior art." 678 F.3d at 1292. The

Court rejected the challenger's assertion of one proposed lead compound as being one of "trillions of carbostyril compounds encompassed by the [prior art]" that might have a "laundry list" of potential effects, only one of which was relevant to the claims (antipsychotic activity). *Id.* at 1293-94. Similarly, another potential lead was ruled out as "one among hundreds of examples" that similarly concerned an "extensive list" of potential effects. *Id.* at 1295. Furthermore, in rejecting the proposed lead compounds at issue, the Court noted that additional modifications to the prior art that would have been needed to arrive at the claimed inventive compound. *Id.* at 1295-96.

But nothing in this Court's precedent, as this Court recognized in *Otsuka* and *Takeda*, decrees that the lead-compound framework universally applies in obviousness challenges involving the chemical arts, even to apparatus or method claims that merely use a particular composition. For example, when a patent does not claim the "compound itself, but rather methods of using the compound," the lead-compound analysis is not required, and "the proper inquiry is whether a person of ordinary skill would have been motivated to modify the prior art" to use a particular compound in a known method. *Novartis Pharms. Corp. v. West-Ward Pharms. Int'l Ltd.*, 923 F.3d 1051, 1060 (Fed. Cir. 2019). So, too, with respect to the apparatus claims at issue; the proper inquiry is whether the POSA would have been motivated to combine the existing art of chromatography matrices with the

teachings of Abrahmsén, Linhult, and Hober that expressly suggest the C(G29A) modification among a finite number of identified, predictable solutions.

Moreover, when genetic modifications with useful properties are identified, applying that modification to appropriate amino acid sequences may involve ordinary skill—particularly when the prior art teaches that application expressly. A POSA in this field—a person with an advanced degree in biochemistry, bioengineering, or related fields; several years of post-graduate training or related experience; "an understanding of the various factors involved in purifying proteins using chromatography"; and "multiple years of experience with affinity ligand design and protein purification," Appx13—is "a person of ordinary creativity, not an automaton." *KSR*, 550 U.S. at 421. Such a POSA, "facing the wide range of needs created by developments in the field of endeavor," *id.* at 424, would as a matter of ordinary skill attempt importing a successful modification from one domain of a protein to one of just four other homologous domains of the ***same*** protein. *See also id.* at 421 ("When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp."). A POSA's skill in this field is not limited to modifying currently used ligands, particularly given the express prior-art teachings.

Those teachings also eliminate any hindsight concerns that underlie the lead-compound doctrine. Both Abrahmsén and Hober expressly disclose making the claimed modification to any one of five domains—which were well-known for their use in chromatography—for the express purpose of avoiding protein degradation in highly alkaline environments. Appx90. Cytiva's attempt to analogize use of natural SPA domains (which are highly homologous) in apparatus claims to this Court's lead-compound cases misses the mark because those cases involved a "panoply," "hundreds," or "trillions" of choices—not five. And those cases certainly do not involve multiple prior art references teaching the claimed invention in a single paragraph. This is not hindsight, *ex post* reasoning, CB 25, 36 (quoting *Otsuka*, 678 F.3d at 1292), but rather an explicit motivation provided by the prior art for a limited set of preferred starting points. For this additional reason, the lead-compound analysis is inapplicable.

Cytiva's fallback is to argue that the starting points for a lead-compound analysis were not limited to the natural SPA domains, and the consequences of the modification were not predictable. CB 35-43. Both arguments fail. *First*, although the universe of potential modified SPA ligands that could theoretically be used in chromatography for any purpose was large, the prior art itself already provided a marker narrowing the selection to "any of" the five natural SPA domains for a ligand for isolating IgG (*i.e.*, the obviousness rationale proposed by JSR). And using the

natural SPA domains as starting points would have made sense—all of the other "starting points" identified by Cytiva are ultimately derived from the naturally occurring, highly similar domains. CB 38 (pointing to Dr. Cramer's testimony regarding Domain Z, which is a G29A mutant of natural Domain B, and Z(N23T), which can be derived from Domain B or C). Furthermore, the rationale for selecting the five natural domains as starting points was supported. In fact, Cytiva does not even challenge the Board's findings that these five domains were known to have affinity for Fc and certain Fab fragments, and that they already had "widespread use" in affinity ligands for capture and purification of antibodies. Appx31-32; Appx3815.

Second, as to predictability, Cytiva complains that protein engineering generally is an unpredictable field. CB 39-42. But "obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art[.]" *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007). And Cytiva attempts to downplay the Board's specific findings that are fatal to its argument. The Board found, based on Abrahmsén's computer modeling, that making the specific G29A modification to Domain C would not be expected to affect IgG binding. Appx38-39 (also discussing Linhult's teachings for reasonable expectation of success); Appx94-97. Cytiva argues this finding does not matter because the Board did not find that a "POSA could predict other properties of an SPA-based ligand with a G29A mutation." CB 42. But Cytiva's demand for absolute predictability of all

properties is unwarranted and untethered from the claim limitations. The Board's factual finding of ***reasonable*** predictability based on Abrahmsén was sufficient to support its conclusion that the G29A modification to one of the five natural domains of SPA was merely one of a "finite number of identified, predictable solutions," rendering the claims obvious. Appx35; Appx90 (quoting *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1070 (Fed. Cir. 2012) (quoting *KSR*, 550 U.S. at 421)).

For these reasons, the Board correctly deemed the lead-compound analysis inapplicable, and properly analyzed obviousness, including under *KSR*. Appx35-37; Appx91-93. This Court should reject Cytiva's attempt to erect additional hurdles designed to confuse a straightforward determination of obviousness given the express teachings in the prior art. Regardless, any such hurdles are easily cleared here, for the reasons below.

C. Even Under a Lead Compound Analysis, Domain C Would Have Been a Lead Compound

1. Each of the Five Native SPA Domains Would Have Been "Lead Compounds"

Even assuming that a lead-compound analysis was needed, as the Board found, the art taught that "[e]ach of '[t]he five SPA domains show individual affinity for the Fc-fragment … as well as certain Fab-fragments of immunoglobulin G (IgG) from most mammalian species.'" Appx31-32 (quoting Appx3815) (second

alteration in original). More specifically, the art taught that, "[d]ue to the high affinity and selectivity of SPA, it has a widespread use as an affinity ligand for capture and purification of antibodies." *Id.* The Board found that "Linhult, therefore, teaches [a] column chromatography matrix that has a SPA domain containing a G29A mutation attached to a chromatography matrix." Appx33. This suffices to show a POSA's motivation to start with "each" of the five SPA domains in creating a chromatography matrix for isolating IgG. *See also* Appx3148-3153; Appx3172-3176; Appx3215; Appx5530-5532.

If the purpose of the lead-compound analysis is, as Cytiva argues, to "winnow" the universe of starting points, CB 39, that universe has been successfully winnowed to include the five natural SPA domains as reasonable and promising starting points based on the express teachings of the prior art. And as explained above, all of the other proposed starting points identified by Cytiva ultimately derive from the natural SPA domains (*e.g.*, Domain Z is merely a variant of natural Domain B). Finally, the "individual affinity" characteristics taught in Linhult (and credited by the Board) are akin to the "positive attributes" mentioned in *Otsuka* for reasons to select a lead compound that are separate from mere structural similarity. *Otsuka*, 678 F.3d at 1292.[7]

[7] The five domains are also highly structurally similar, as the Board correctly found and is not disputed. Appx37.

Cytiva's suggestion that the Z domain or Z(N23T) would have been a lead compound is irrelevant, *see* CB 26-29, and ironic given that the G29A modification had already been applied there. The question is whether a POSA would have viewed the C domain as a potential starting point, whether or not it was the ***only*** one. *See Altana Pharma AG v. Teva Pharms. USA, Inc.*, 566 F.3d 999, 1008 (Fed. Cir. 2009) (upholding identification of 18 exemplary lead compounds because prior art need not "point to only a single lead compound"); *see also Purdue Pharma Prod. L.P. v. Par Pharm., Inc.*, 377 F. App'x 978, 982 (Fed. Cir. 2010) (one of fourteen compounds was sufficiently specific). And as the Board correctly found, even though the exemplary embodiments in those references were regarding Domain Z—a B(G29A) mutant—and other variants of natural domains, the prior art is "available for all that it discloses and suggests to one of ordinary skill in the art," not just the preferred embodiments. Appx34.

Cytiva repeatedly attempts to discredit these disclosures on appeal through adjectives—calling them "general," "fleeting," or "passing" teachings. CB 18, 19, 23, 27, 33, 54. But the teaching to apply the G29A modification to "any of the E D A B C domains" is unambiguous and expressly taught in two separate references. *See supra* at 26. Cytiva has no answers to these teachings on the merits, and instead accuses the Board of picking and choosing only part of a reference. CB 31 (citing *In re Wesslau*, 353 F.2d 238, 241 (C.C.P.A. 1965)). But Cytiva's demand that the

prior art teaching relates to the embodiments or experiments in the reference is contrary to this Court's precedents, as the Board correctly recognized. Appx34 (citing *In re Lamberti*, 545 F.2d 747, 750 (C.C.P.A. 1976)); *see* CB 28 (pointing to deposition testimony in which Cytiva is focused on "experiments that [the prior art] actually performed," Appx6278-6279). This Court should reject Cytiva's attempts—through its attempted invocation of the lead-compound test—to circumvent this Court's precedent that the prior art teachings are not limited to their embodiments, but are available for all they disclose to a POSA.

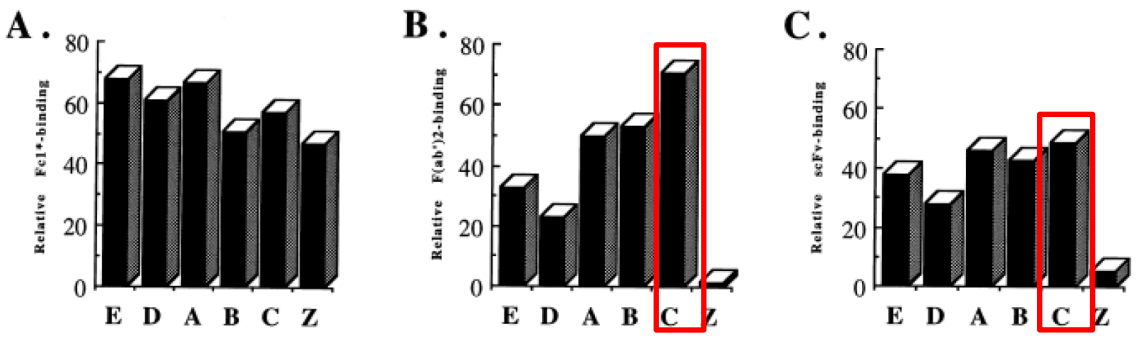
Thus, to the extent the Court determines that a lead-compound analysis was necessary, remand would be futile here because the Board has already made sufficient factual findings to conclude that each of the natural SPA domains would have been a suitable lead compound.

2. Domain C Itself Is a Lead Compound

Even if a lead compound analysis were legally required, the prior art also pointed to Domain C individually as a promising starting point. JSR showed that modifications tested in Linhult (*e.g.*, N23T) were based on Domain C, and thus the prior art pointed to Domain C as a promising starting point. Appx1791-1793; Appx3817-3820 (Linhult explaining substitutions were made based on homologies with other natural domains and testing Z(N23T), which was "the most promising candidate" derived from homology with Domain C); Appx437-438 (describing

Linhult's top-performing ligands as containing the "obvious" modifications, N23T and N43E, based on the homologous C domain); Appx1854; Appx5402 (125:18-126:12) (Cytiva's expert agreeing the choices in Linhult were based on homologies); Appx3851 (Hober explaining that the N23T ligand was "the best embodiment"). Indeed, Cytiva's own prior art commercial product—MabSelect™—utilized Domain C (along with the other naturally occurring domains) in a chromatography matrix and has done so since 2001, undermining its arguments that no POSA would have considered Domain C as a promising lead for such matrices. Appx5531-5532.

Cytiva wrongly attempts to promote Fab-fragment binding as an overriding concern that would have driven a POSA's decision-making. *See* CB at 41-42. But even taking this motivation at face value, Cytiva's own references and its expert evidenced reasons why a POSA would have selected Domain C as a lead compound. For instance, Jansson reveals that Domain C showed the highest level of Fab binding among the natural domains:



Appx7373 (annotations added). And Cytiva's expert, Dr. Bracewell, testified that, "[i]f my sole objective was to look for Fab-binding, C Domain seems the most promising." Appx5428 (229:16-230:15). To the extent that, as Cytiva repeatedly argues, a POSA would have been motivated by a desire for Fab binding, in Dr. Bracewell's own words, Domain C was "the most promising" starting point. *Id.*

JSR also presented additional evidence below showing an explicit preference for Domain C as a starting point. Specifically, Berg taught that Domain C is one of two "prefer[red]" domains for modifications to be used in such chromatography ligands. Appx4166 ("Thus, the ligands may comprise one or more of Domain A, B, C, D and E, preferably Domain B and/or Domain C."); *see also* Appx505; Appx516; Appx522; Appx533; Appx3490-3494. Cytiva's response on the merits is only (i) its now-familiar refrain that this express teaching is a "fleeting reference," CB 33, and (ii) attempting to improperly limit Berg's teaching to its embodiments, CB 34 (pointing to what Berg purportedly "focuses on").

Berg provides an alternative basis for affirmance because the Court can determine its prior art status as a matter of law. *See ATEN Int'l Co. v. Uniclass Tech. Co.*, 932 F.3d 1364, 1367 (Fed. Cir. 2019) ("Whether a reference is prior art is a question of law based on underlying factual questions."). Cytiva never disputed any underlying facts regarding Berg's qualification as § 102(b) prior art, instead raising arguments only under § 102(a) that Berg was not "by another." Appx 1592-1595;

Appx2151-2154; *see also* Appx1979-1984; CB 33. Cytiva also argued that reliance on Berg's status as § 102(b) art was presented too late in the proceeding. Appx2154-2155. But Cytiva was given the opportunity to respond to the argument that Berg was § 102(b) art in both its Sur-reply and at the oral hearing—it simply had no answer on the merits. Its procedural argument rings hollow, and remand to provide Cytiva another opportunity to respond would be futile.

If the Court determines, however, that underlying factual disputes are at issue, the proper course would be for the Court to remand for the Board to decide those in the first instance. The Board did not make any merits determinations as to Berg in its final written decisions finding unpatentability. Appx51 ("not reach[ing] these additional asserted grounds"). For all the foregoing reasons, however, this Court should affirm the Board's unpatentability ruling outright.

III. THE COMPOSITION FAB BINDING CLAIMS, WHICH MERELY CLAIM AN INHERENT PROPERTY OF THE OBVIOUS C(G29A) LIGAND, ARE UNPATENTABLE[8]

The relevant question is whether a patentee can escape obviousness by claiming an inherent property of a known or obvious compound. Precedent squarely answers this question: no. The Board correctly held that the inherent property of Fab binding did not confer patentability. This Court should affirm.

[8] These arguments relate to claims 4 and 17 of the '765 patent at issue in IPR2022-00036 and -00043.

A. Reasonable Expectation of Success Analysis Is Unnecessary for a Dependent Claim Limitation That Recites Only an Inherent Property of an Otherwise Obvious Composition

Cytiva has conceded that Fab binding is an inherent property of a C(G29A) ligand, as the Board found. CB 44; Appx2289; Appx48. The C(G29A) ligand (and all of the limitations of the independent claims) would have been obvious for the reasons found by the Board and explained above. Cytiva nevertheless argues that its dependent claims reciting that the C(G29A) ligand of the independent claims "is capable of binding to the Fab part of an antibody" are patentable because this inherent property would have been unexpected. But the Board correctly recognized that, as is the case here, inherent features in obvious compositions do not render the claims patentable. Appx46 (citing *In re Pearson*, 494 F.2d 1399, 1403 (C.C.P.A. 1974); *Persion Pharms. LLC v. Alvogen Malta Operations Ltd.*, 945 F.3d 1184, 1190 (Fed. Cir. 2019)). Those and other precedents foreclose Cytiva's patentability charge.

1. A POSA Need Not Reasonably Expect Success in Achieving an Inherent Property of an Obvious Composition

Persion involved claims for a method of treating pain in patients with moderate liver failure (hepatic impairment) using an extended-release formulation of hydrocodone. 945 F.3d at 1187. The claims included limitations reciting inherent pharmacokinetic properties. *Id.* at 1190-91. This Court confirmed that inherency can satisfy a claim limitation in an obviousness analysis where it is "the natural result

of the ***combination of prior art elements***." *Id.* at 1191 (emphasis original) (quoting *Par Pharm.*, 773 F.3d at 1194-95). Because it was obvious to treat the patient with the formulation, the inherent pharmacokinetic limitations were entitled to "no patentable weight" and could not defeat obviousness. *Id.*; *see also Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1354 (Fed. Cir. 2012) ("[A]n obvious formulation cannot become nonobvious simply by administering it to a patient and claiming the resulting serum concentrations. To hold otherwise would allow any formulation—no matter how obvious—to become patentable merely by testing and claiming an inherent property.") (citation omitted).

That logic directly applies here. The claimed ligand was an obvious modification of Domain C in light of the prior art teachings to make this modification. Appx31-44. The natural result of this modification is the capability to bind to the Fab part of an antibody, as recited in the dependent claims. *Persion*, 945 F.3d at 1191; *see also Par Pharm., Inc. v. TWI Pharms., Inc.*, 773 F.3d 1186, 1195-96 (Fed. Cir. 2014).

Cytiva unpersuasively attempts to distinguish *Persion* because allegedly "the prior art taught directly … towards the use of a particular formulation in a particular patient population," and therefore "the combination of art before the district court gave the POSA a reason to practice the specific claimed method," as opposed to "a whole class or category of methods." CB 56-57. That is a distinction without a

difference; so long as a POSA has a reason to make the claimed combination, and the inherent property is thereby obtained, the claim is obvious. The relative strengths of the motivation to combine in various cases is immaterial. Regardless, the prior art here taught directly making a particular modification (G29A) to a particular domain (Domain C).

Pearson declares the same principles. In *Pearson*, the patentee was attempting to claim a prior-art calcium composition by claiming a new use (preventing "pops" and "unsound kernels" for peanut farming). 494 F.2d at 1402. The Court held that the claim "terms merely set forth the intended use for, or a property inherent in, an otherwise old composition," and that "such terms do not differentiate the claimed composition from those known to the prior art." *Id.* at 1403. Again, that logic directly applies—Cytiva's Fab-binding composition claims merely set forth a property inherent in the matrix composition claims determined to be obvious. In the CCPA's words, Cytiva is attempting to patent an otherwise unpatentable composition by "labeling its container" for an allegedly different (Fab-binding) use. *Id.* "The container … still contain[s] the old composition," and thus is unpatentable. *Id.*

Cytiva points to dicta in *Pearson* as "emphasiz[ing] the limits of its inherency analysis," CB 55-56, but not in any way germane to this case. The *Pearson* court observed that "terms which recite the intended use or a property of a composition"

might "be used to distinguish a new from an old composition" ***if*** "such terms … define, indirectly at least, some characteristic not found in the old composition." 494 F.2d at 1403. It gave the hypothetical example of "calcium compounds of very small particle size [which] had not been known to the prior art" that, "when applied to the foliage of a peanut crop[,] will substantially reduce the formation of pops and unsound kernels." *Id.* (quoting contested composition claim). In other words, had the patentee invented a new type of calcium (having very small particle size), it could choose to define that composition through its function. By contrast, here, Cytiva does not "define … some characteristic not found in the" obvious C(G29A) ligand—it does not describe some further modification or form of the composition not known in the art. *Id.* The Fab-binding characteristic is inherent in the obvious combination, and thus lacks patentable weight.

This Court's decision in *Hospira, Inc. v. Fresenius Kabi USA, LLC*, 946 F.3d 1322, 1332 (Fed. Cir. 2020), tracks the logic in *Persion* and further confirms the Board's decision. The *Hospira* claim recited a pharmaceutical composition at a certain concentration that was of a specified stability—it "exhibits no more than about 2% decrease in the concentration" over five months. *Id.* at 1326-27. The Court affirmed the district court's conclusion that the claim was obvious based on the district court's finding of the inherency of the 2% stability property. *Id.* at 1329-31. But this Court faulted the district court for conducting the "unnecessary

analysis" of whether a POSA would "have had a reasonable expectation of successfully achieving the about 2% limitation." *Id.* at 1331-32. "If a property of a composition is in fact inherent, there is no question of a reasonable expectation of success in achieving it." *Id.* at 1332.

Cytiva's discussion of *Hospira* strictly avoids discussing the portion that applies directly to this case. CB 57-58. Instead, Cytiva emphasizes that the *Hospira* patentee had not contested (on appeal) the district court's factual finding of reasonable expectation of success. Instead, the patentee argued that the district court improperly drew an inference of stability from extrinsic evidence, and that the court should have determined whether the stability property was necessarily present in the patented invention (as opposed to having only a reasonable expectation of success). *Id.*; *Hospira*, 946 F.3d at 1331. But that does not change the *ratio decidendi* of this Court; it held that the district court properly found inherency and, once it had done so, the district court's further analysis of reasonable expectation of success in achieving a combination with the inherent property was unnecessary (not that the patentee waived the latter issue on appeal). *Hospira* thus rejects the very test Cytiva demands—namely, that a fact finder must find that a POSA in making a combination would have had a reasonable expectation of success in achieving an inherent property.

Finally, the Court's recent *In re Couvaras* decision supports rejecting inherent features as imparting patentability, even when they are argued to be unexpected. 70 F.4th 1374 (Fed. Cir. 2023). There, the patentee, like Cytiva, argued that an inherent mechanism of action, *i.e.*, "increased prostacyclin release," should have patentable weight because it was unexpected. *Id.* at 1380. This Court disagreed, holding that "[r]eciting the mechanism for known compounds to yield a known result cannot overcome a prima facie case of obviousness, even if the nature of that mechanism is unexpected." *Id.* (citing *In re Montgomery*, 677 F.3d 1375, 1381 (Fed. Cir. 2012) and *In re Huai-Hung Kao*, 639 F.3d 1057, 1070-71 (Fed. Cir. 2011)). *Couvaras* disposes of Cytiva's challenge.

Faced with this wall of precedent, Cytiva spins a new supposed rule in which inherency can ***sometimes*** be used to show an inherent feature in an obvious composition based on the breadth of the prior art disclosures rendering the composition obvious and the "value for the public." CB 53. Precedent rejects this murky and unworkable public-value test. But even if it applied, Cytiva's claims would fail this test: "[W]here the teachings of the [Abrahmsén, Hober, and Linhult] art would have pointed the POSA in the direction of a claimed [C(G29A)] composition for reasons [alkaline stability] other than the inherent property [Fab binding], a patentee's claims drawn to the undisclosed, inherent features of such composition may add little or no value for the public." *Id.*

2. Cytiva Relies on Inapposite Precedents That Do Not Support Its Position

Cytiva also cites a slew of cases—many of which were never cited to the Board—in support of its view that an unexpected inherent property can defeat obviousness. *Compare* CB 45-59, *with* Appx1431-1432. The short answer, as discussed above, is that cases like *Couvaras* reject that proposition. But Cytiva is also mistaken in its analysis of the cited precedents, which stand for the irrelevant proposition that an unexpected inherent property cannot supply or defeat a motivation to combine.

Cytiva misplaces reliance on *Honeywell International Inc. v. Mexichem Amanco Holding S.A. DE C.V.*, 865 F.3d 1348 (Fed. Cir. 2017). There, the patentee Honeywell challenged the PTAB's obviousness ruling on the grounds that a POSA would not have been motivated to combine a particular hydrogen-compound refrigerant ("HFO-1234yf") and a particular lubricant ("PAG") with a reasonable expectation of success. *Id.* at 1353. Honeywell had submitted evidence that both HFO refrigerants and PAG lubricants were known to be unstable. *Id.* at 1351, 1353. Therefore, Honeywell argued that the prior art would not have led a POSA "to combine HFO-1234yf, one of a disfavored class of refrigerants, with a PAG lubricant, known to be unstable," and thus a POSA "would have expected the combination to result in peroxide formation that leads to degradation reactions of HFO compounds that are not possible with the prior art saturated HFC compounds."

Id. at 1351. The combination surprisingly resulted in miscibility/stability, and Honeywell argued that this was a secondary indicium of nonobviousness. *Id.* at 1353.

This Court agreed with Honeywell, and found that "the Board committed legal error by improperly relying on inherency to find obviousness and in its analysis of motivation to combine the references." *Id.* at 1354. Specifically, "the Board erred in relying on inherency to dismiss evidence showing unpredictability in the art—evidence which it later acknowledged did persuasively demonstrate unpredictability—in order to reject Honeywell's argument that one of ordinary skill would not have been motivated to combine the references with a reasonable expectation of success." *Id.* (emphasis omitted) This Court observed the unknown inherent stability of the combination did not contradict Honeywell's evidence that a POSA would not have been motivated to combine HFO-1234yf with a PAG lubricant because of their known instability and expected degradation. "Because finding a motivation to combine the references and consideration of objective evidence are fact questions," the Court remanded to the Board to consider those questions free of its legal error. *Id.* at 1356.

Honeywell is inapposite to the dependent claims, where the motivation to combine is not at issue. Judge Bryson explained just that point when sitting by designation in *Pernix Ireland Pain DAC v. Alvogen Malta Operations Ltd.*, the

district court case reviewed in *Persion*. *See Pernix*, 323 F. Supp. 3d 566, 607 (D. Del. 2018), *aff'd sub nom. Persion Pharms. LLC v. Alvogen Malta Operations Ltd.,* 945 F.3d 1184 (Fed. Cir. 2019). Like Cytiva, the patentee in *Pernix* relied on *Honeywell* to argue that the unexpected character of an inherent property (there, the pharmacokinetic properties of using an extended-release formulation of hydrocodone) defeated obviousness. *Pernix*, 323 F. Supp. 3d at 575-76. Judge Bryson rejected the patentee's reliance on *Honeywell* "because that case involved using an unknown but inherent property ***as a teaching*** in an obviousness analysis." *Id.* at 606-07. *Honeywell* "did not involve a [claim] limitation that recites an inherent property," *id.*, and "[t]he Federal Circuit's cases demonstrate that necessarily present properties, such as the pharmacokinetic parameters of previously known compositions, do not add patentable weight when they are claimed as limitations," *id.* at 605. *Honeywell*, Judge Bryson explained, simply vacated the Board's obviousness analysis because it "ignored the unpredictability in the art and erroneously relied on inherent but unknown properties in finding a motivation to combine." *Id.* at 607. This Court in *Persion* upheld the district court's obviousness finding without questioning its analysis of *Honeywell*. *Persion*, 945 F.3d at 1190-91.

Cytiva also misses the mark in relying on *In re Spormann* for the proposition that "[o]bviousness cannot be predicated on what is unknown." CB 50 (quoting *In*

re Spormann, 363 F.2d 444, 448 (C.C.P.A. 1966)). *Spormann*, like *Honeywell*, establishes that an unknown inherent property cannot establish the motivation to combine necessary for obviousness. 363 F.2d at 447-48 (inherent property of sulfate minimization did not mean that it would have been "obvious to one of ordinary skill in this art to conduct the old reaction by such spraying under all the conditions set out in the claims and obtain appellants' results"). That does not mean that a limitation reciting merely an inherent feature of a combination that is obvious for reasons other than the inherent feature can confer patentability.

On appeal, Cytiva also relies on *In re Rinehart*, 531 F.2d 1048 (C.C.P.A. 1976), a case it never mentioned to the Board. *Rinehart* does not apply, and once again Cytiva snips phrases out of context without analyzing the case as a whole.

Rinehart involved "method[s] for the commercial scale production of polyesters" while maintaining a certain glycol-acid ratio. *Id.* at 1049. The obviousness question was whether two references (Pengilly and Munro) could be combined with a reasonable expectation of success: *i.e.*, "whether it would have been obvious, in scaling up Pengilly's process, to have employed Munro's higher pressures or in scaling up that of Munro to have employed Pengilly's preformed polyester." *Id.* at 1053. This Court's predecessor found that "[t]he tribunals below did not meet the requirement of establishing some predictability of success ***in any attempt to combine elements of the reference processes in a commercial scale***

operation." *Id.* at 1053-54. The inherency of "success" (the commercial scale of the combined process) did not establish the reasonable success of the combination because "[i]nherency and obviousness are entirely different concepts." *Id.* at 1054. As the Court explained, neither prior-art reference "suggest[ed] a solution" to problems that would have been encountered in any attempted process scale-up, as required by the claims. *Id.* (discussing problems of lengthened reaction times and frozen polymer lumps). Thus, that the prior-art combination would have resulted in a claimed process that could operate at commercial scale (*i.e.*, was inherent) did not render the claims unpatentable when a POSA would not have been motivated to combine the two processes in the first place. *Id.*

Rinehart is thus an inapposite motivation-to-combine case.[9] Here, the additional requirement of "capability of binding the Fab part of an antibody" does not impact the workability of making a G29A modification to the C domain to create a ligand for use in a chromatography matrix. No additional, undesirable, or forbidden changes to the system (such as increasing the glycol-acid ratio in *Rinehart*) are required. And here, a POSA would have been motivated to make the C(G29A)

[9] *Millennium Pharmaceuticals, Inc. v. Sandoz Inc.* is equally inapposite and similarly addressed whether inherency can provide a motivation to combine. 862 F.3d 1356, 1364, 1367 (Fed. Cir. 2017) ("nothing on the record teaches or suggests that a person of ordinary skill should have used mannitol as part of a synthetic reaction to make an ester through lyophilization").

modification with a reasonable expectation of success to increase alkaline stability of the ligand. The Fab binding capability is merely the natural result of the obvious prior art combination, as in *Persion*, *Hospira*, and *Couvaras*, and the Fab-binding capability does not impact the underlying obviousness of creating the C(G29A) ligand, unlike *Rinehart*.[10] For the foregoing reasons, the Court should reject Cytiva's insistence that the Board make an explicit reasonable expectation of success finding as to the Fab-binding limitation that is inherent in the obvious C(G29A) ligand.

B. Cytiva's Alleged Unexpected Results Do Not Overcome the Strong Case of Obviousness

Before the Board, Cytiva argued objective indicia in two-and-a-half pages of its Patent Owner's Response, Appx1432-1434, completely dropping this issue in its Sur-reply. It also failed to address it at the oral hearing, even though JSR did. Appx2221-2222. This underdeveloped argument by Cytiva did not overcome the strong obviousness case, and the Board was correct in rejecting it. Appx48-49. Regardless, this argument is now foreclosed by *Couvaras*.

[10] Cytiva cursorily cites a number of other cases, but all are distinguishable as either involving factual disputes over inherency (which is not disputed here) or not involving dependent claim limitations reciting inherent properties. *See* CB 45-46 (citing cases).

1. Unexpected Results Stemming from an Inherent Property of an Otherwise Obvious Combination Do Not Establish Nonobviousness

The Board determined that JSR persuasively showed why the claimed C(G29A) ligand would have been obvious—a POSA would have been motivated to make the G29A modification to "any one" of the natural SPA domains for alkaline stability and would have reasonably expected success in binding IgG. Appx48. Because the C(G29A) ligand would have been obvious, the Board correctly determined that JSR did not need to additionally prove that "the inherent characteristic of the Fab binding needed to be recognized in order to arrive at the conclusion that the recited structure in claim 1 would have been obvious." Appx48-49. This was because, as the Board had already found, "[t]he 'capable of binding' language of claim 4 … does not add any structural limitations to claim 1[;] it merely recites the function of the composition when used for example in an assay." Appx46. As such, the Board correctly cited the principle in *Persion* that "it is not the law that a structure suggested by the prior art, and, hence, potentially in the possession of the public, is patentable because it also possesses an inherent, but hitherto unknown, function which the patentees claim to have discovered." 945 F.3d at 1190 (cleaned up); *see also* Appx49 (quoting this portion of *Persion*). That is exactly what Cytiva is trying to do here—claim the C(G29A) "structure suggested by the prior art … is patentable … because it also possesses an inherent, but [allegedly] hitherto

unknown, function [of Fab binding] which [Cytiva] claim to have discovered." *Id.* That is "not the law." *Id.*

Cytiva's response is only to knock down a strawman, pointing to a different section in *Persion* and contending that *Persion* "nowhere suggested that 'inherency' could be used to ignore or discount the existence of unexpected properties as objective evidence of nonobviousness." CB 63-64. But that's exactly what *Persion* held in the portion quoted by the Board and ignored by Cytiva, as discussed immediately above. In fact, this Court concluded that "the pharmacokinetic limitations of the asserted claims were inherent and added ***no patentable weight*** to the pharmacokinetic claims." 945 F.3d at 1191. As discussed above, an unexpected property may, in a given circumstance, underscore the lack of motivation of a POSA to combine prior art teachings; but if such a motivation is established, as it is here, the unexpected nature of an inherent property is not probative of nonobviousness.

Cytiva's observation that the Court later considered the objective indicia, including "unexpected results," CB 64, is of no moment. The Court's objective indicia analysis focused on the nonobviousness of the claim limitation requiring that the "dose is not adjusted." 945 F.3d at 1194 (discussing objective indicia regarding "not requir[ing] a dose adjustment for hepatically impaired patients"); *see also id.* at 1187 (claim 1 reciting "the starting dose is not adjusted relative to a patient without hepatic impairment"); *Pernix*, 323 F. Supp. 3d at 615-16 (district court discussing

alleged unexpected results related to dose adjustment). The unexpected benefits of not adjusting the dose was relevant to the obviousness of the combination; the Court did not suggest that the separate, inherent pharmacokinetic properties, which the Court had found "added no patentable weight," *Persion*, 945 F.3d at 1191, themselves suggested nonobviousness. That is just a matter of logic; if it is otherwise obvious to make a certain combination, the fact that the combination has certain inherent properties does not somehow make the combination nonobvious. For the reasons described in *Persion*, this Court should reject Cytiva's argument that the unexpectedness of Fab binding (even if true) adds patentable weight to the dependent claims.

Regardless, *Couvaras* disposes of Cytiva's contentions. The patentee argued that the increased prostacyclin resulting from the claimed co-administration of two antihypertensive agents was unexpected, and that "the Board erred by nonetheless giving no weight to the unexpected results indicium of nonobviousness." 70 F.4th at 1380. This Court rejected the argument because, as it had discussed with regard to expectation of success, "recitation of a mechanism of action, even an unexpected one, does not necessarily overcome a prima facie case of obviousness." *Id.*; *see also In re Pasteur*, Appeal No. 2022-1896, 2023 WL 8609987, at *5 (Fed. Cir. Dec. 13, 2023) (same).

2. Cytiva's Alleged Unexpected Results Are Insufficient to Overcome JSR's Strong Showing of Obviousness

Even if consideration of this inherent property were relevant, which it is not, Cytiva's nonobviousness challenge lacks merit. To be probative of nonobviousness, "unexpected results must establish that there is a ***difference between the results obtained and those of the closest prior art***, and that the difference would not have been expected by one of ordinary skill in the art at the time of the invention." *Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc.*, 752 F.3d 967, 977 (Fed. Cir. 2014). Cytiva never attempted to compare the results of the C(G29A) ligand to the C domain (which would have been the closest prior art and was known to have Fab binding (Appx7373; Appx5428 (229:16-230:15))). Thus, Cytiva's unexpected results argument is facially deficient. *See* Appx2221-2222; *see also* Appx384 (Cytiva's '142 patent pointing to Jansson as "show[ing] that all the individual SpA domains also bind certain antibodies at the Fab region").[11]

Furthermore, even if, *arguendo,* there were any merit to Cytiva's unexpected results argument (there is not), remand would be futile. The ultimate issue of obviousness is reviewed de novo, and Cytiva's weak showing of unexpected results does not overcome the strong prima facie case. *See Bayer Pharma AG v. Watson*

[11] Cytiva cannot remedy that deficiency on appeal. Regardless, Cytiva's opening brief contains no such comparison, and instead cites only its own brief discussing the alleged general unpredictability of protein engineering. CB 62-63 (citing CB 10, 39-40, 45-47).

Lab'ys, Inc., 874 F.3d 1316, 1328-29 (Fed. Cir. 2017) (even if copying and unexpected results "weigh in favor of … nonobviousness," the district court clearly erred in finding nonobviousness due to the "repeated suggestion in the prior art" to make the claimed invention, which provided "strong [motivation] evidence"). As a matter of law, the "repeated suggestion" from both Abrahmsén and Hober to make the G29A modification to any of the natural SPA domains provides "strong evidence of a motivation to make the claimed combination," rendering the claims obvious. *Id.*; *see also Allergan, Inc. v. Sandoz Inc.*, 726 F.3d 1286, 1293 (Fed. Cir. 2013) (similarly holding unexpected results to be insufficient in light of other evidence of obviousness); Appx3138-3160; Appx3164-3167; Appx3203-3222; Appx3227-3229.

Cytiva includes a large string cite for the proposition that "it does not matter whether the unexpected feature was inherent in the invention," and then charges the Board with "ignor[ing] this precedent." CB 61-62. This argument is now foreclosed by *Couvaras*, but notably Cytiva did not raise ***even one*** of these cases to the Board in its unexpected results argument. *Compare* CB 61-62 *with* Appx1432-1434. None of those cases warrant reversal.

Honeywell, as discussed in Section III.A.2 above, is distinguishable as a motivation-to-combine case. As the *Honeywell* Court explained, a POSA would not have even have been motivated to combine the claimed ingredients if it could not be

predicted whether they would mix properly or be stable when mixed. *Honeywell*, 865 F.3d at 1354. Because these key properties of the claimed combination were unpredictable, the Court held that the Board erred in dismissing the inherent properties without considering the impact of their unpredictability and unexpectedness on the motivation inquiry. *Id.* at 1354-55. Here, by contrast, Cytiva does not assert unpredictability or uncertainty in being able to achieve the combination of the G29A modification with a C domain, but instead argues unpredictability of an inherent function (Fab binding) of that ligand once created.

Cytiva's citation of *Allergan, Inc. v. Sandoz Inc.*, 796 F.3d 1293 (Fed. Cir. 2015), is even further afield. There, the Court found that "the prior art did not disclose, either explicitly or implicitly, the claimed formulation," and that a POSA "would not have had a reason to select the claimed formulation from the prior art ranges." *Id.* at 1307. But here, both Abrahmsén and Hober expressly disclosed C(G29A). Thus, *Allergan* is inapposite, as it was "not a case where the claims merely recite the unknown properties of an otherwise obvious formulation." *Id.* None of the other cited cases advances Cytiva's position and warrant discussion.

In sum, Cytiva cites a raft of distinguishable cases that it never cited to the Board, faults the Board for not addressing these uncited cases, and fails to persuasively address the on-point precedent cited by the Board. This Court should affirm.

CROSS-APPEAL ARGUMENT

The dependent method claims of the patents at issue recite a method of isolating target compounds using a C(G29A) ligand, "wherein the ligand binds to the Fab part of an antibody." Appx391 (claims 1 and 4). Although it correctly ruled all of the matrix claims and the independent method claims unpatentable, the Board erred in upholding the dependent method claims for three independent reasons.[12]

First, the dependent method claims are invalid for the same reason as the dependent matrix claims. The claimed Fab binding is merely, as Cytiva concedes, an inherent feature of the obvious chromatography method using the C(G29A) ligand of the independent claims, and thus nothing further needed to be proven. Appx443-444. The Board went awry because it misconstrued the dependent method claims to be limited to processes for isolating Fab fragments, and improperly required proof that a POSA employing the method would reasonably expect success in having the C(G29A) ligand bind to Fab fragments.

Second, even under the Board's unfounded construction, a POSA would have found it obvious to create a combination ligand—as expressly taught in Hober—composed of a C(G29A) unit and one of the natural SPA domains, which would have ensured (to the extent there was any doubt) that the matrix possessed some Fab-

[12] The claims involved in JSR's cross-appeal are claims 4 and 7 of the '142 patent (at issue in IPR2022-00041 and -00044) and claims 11 and 29 of the '007 patent (at issue in IPR2022-00042 and -00045).

binding capability. Appx444-445. The Board entirely overlooked JSR's alternative unpatentability rationale based on Hober's combination monomer teachings. The evidence on this point is one-sided, and the Court can reverse. At a minimum, it was error for the Board to skip this unpatentability rationale, and the Court should remand for the Board to determine this issue in the first instance.

Third, Fab binding would have been obvious based on Linhult's disclosures that each of the natural SPA domains show affinity for "certain Fab-fragments," and the fact that it would also be desirable to "purify therapeutics constructed from Fab fragments." Appx444. Because there is no threshold level of binding required by the claims or taught in Cytiva's patent specifications, a POSA would have had a reasonable expectation of success in achieving some minimal amount of Fab binding, which is all Cytiva's claims require. This Court should reverse the Board's decision on this basis, and at a minimum vacate and remand.

I. THE BOARD IMPROPERLY RESTRICTED THE DEPENDENT METHOD CLAIMS TO ISOLATING FAB FRAGMENTS IN FINDING NONOBVIOUSNESS

A. The Method Claims Require That the Ligand "Binds to the Fab Part of an Antibody," Not Fab Fragments

The Board misunderstood the Fab binding method claim requirements, which led to the Board requiring JSR to prove an expectation of success in achieving a feature not strictly required by the claims. Specifically, the Board incorrectly understood the "target compound(s)" of the dependent claims to be limited to "Fab

fragments." Appx102. Claim 1 and dependent claim 4 of the '142 patent are exemplary and recite:

> 1. A process for ***isolating one or more target compound(s)***, the process comprising:
>
> (a) contacting a first liquid with a chromatography matrix, the first liquid comprising the target compound(s) and the chromatography matrix comprising …
>
> (ii) at least one ligand coupled to the solid support …
>
> (b) adsorbing the target compound(s) to the ligand ….
>
> 4. The process of claim 1, wherein the ligand ***binds to the Fab part of an antibody***.

Appx391 (claims 1 and 4).

In evaluating the obviousness of the claims, the Board inexplicably restricted the "target compound(s)" of the claimed process to isolation of Fab fragments, even though neither party advocated such a construction. The Board stated, "Because claim 4 is directed to 'a process for isolating one or more target compound(s)' ***and identifies that the target compound is "the Fab part of an antibody***" [Appx391] (15:63–64), the prior art needs show a reasonable expectation that a mutated SPA ligand binds Fab." Appx102 (footnote omitted). The Board then framed the relevant inquiry as "Petitioner need[ing] to establish that a mutated SPA domain would reasonably bind a Fab ***fragment***." *Id.*

There is no basis for the Board's restriction of claim scope. The Board cites nothing other than the claim itself in support of that restriction. But the claim

nowhere recites a Fab ***fragment***, let alone that such a fragment is the "target compound." To the contrary, the Board's restriction defies the plain claim language, which covers any "process for isolating one or more target compound(s)," without limitation. Appx391. And the specification defines target compounds broadly, to include whole antibodies:

> The target compound(s) ***may be any organic compound, biomolecule or other biological material, such as proteins, e.g. antibodies***; peptides; cells, such as eukaryotic and prokaryotic cells; nucleic acids, such as DNA, e.g. plasmids, and RNA; virus; etc. In an advantageous embodiment, the target compound(s) is ***one or more monoclonal or polyclonal antibodies, such as IgA, IgD, IgE, IgG, and IgM***. In one embodiment, the target compound is a fragment of an antibody, such as a Fab fragment. In yet another embodiment, the target compound is a fusion protein wherein at least one part is an antibody or an antibody fragment.

Appx388 (9:23-34). A process of isolating a Fab fragment is simply one embodiment of the invention—and not even a preferred one. The Board committed "one of the cardinal sins" of claim construction in *sua sponte* restricting the claim to a single embodiment. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1320 (Fed. Cir. 2005) (en banc). Indeed, even Cytiva did not press this construction to the Board; all Cytiva argued below is that the "specification makes clear" that Fab fragments are "includ[ed]" within the term "target compound(s)." Appx1495 (citing Appx380 (Abstract)).

As a result of this claim construction error, the Board unduly focused on whether the ligand would be expected to bind to a Fab fragment. Appx102. But that is not what the claims require. The claims instead merely require that "the ligand binds to the Fab part of an antibody." Appx391. Indeed, the specification includes an express definition making clear that a Fab-binding ligand can bind either "full antibodies" or "antibody fragments":

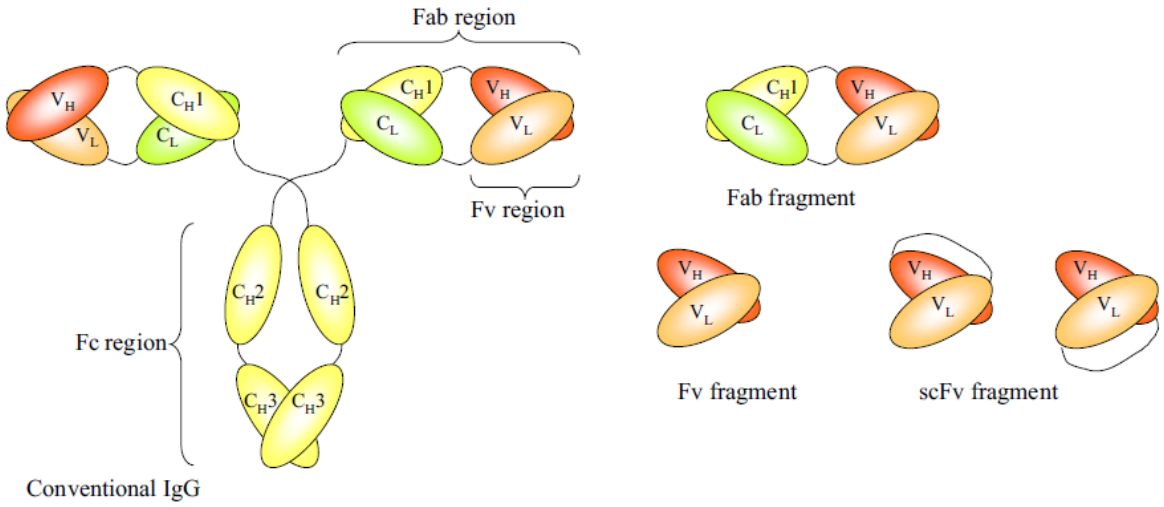
> DEFINITIONS
>
> …
>
> The term "Fab fragment" refers to the variable part of an antibody; hence a "Fab-binding ligand" is capable of binding to either full antibodies via Fab-binding; or to antibody fragments which includes the variable parts also known as Fab fragments.

Appx385 (4:39-58); Appx6286 (154:21-155:9); Appx2208-2209. The Board could not disregard the patent's lexicography. *Liebel-Flarsheim Co. v. Medrad, Inc.*, 358 F.3d 898, 913 (Fed. Cir. 2004); *Parkervision, Inc. v. Vidal*, 88 F.4th 969, 976-78 (Fed. Cir. 2023). Thus, claim 4 (and the other dependent method claims) encompasses processes to isolate any target compound, including whole antibodies, and for such processes the claim is satisfied if the ligand binds to the Fab part of the intact antibody.

B. Under the Correct Construction, the Fab Binding Claims Merely Recite an Inherent Feature of an Obvious Process

The Board's claim construction error infected its obviousness analysis of the dependent method claims. Even if, *arguendo*, a process to isolate Fab fragments were nonobvious, as the Board found, claim 4 is still invalid so long as any process covered by the claim is obvious. It is a "long-established rule that claims which are broad enough to read on obvious subject matter are unpatentable even though they also read on nonobvious subject matter." *In re Cuozzo Speed Technologies, LLC*, 793 F.3d 1268, 1281 (Fed. Cir. 2015) (cleaned up); *In re Lintner*, 458 F.2d 1013, 1015 (C.C.P.A. 1972); *Unwired Planet, LLC v. Google Inc.*, 841 F.3d 995, 1002 (Fed. Cir. 2016) ("It is enough that the combination would sometimes perform all the method steps ….").

Because claim 4 is broad enough to encompass a process of isolating a target compound of a whole antibody (including IgG), claim 4 would have been obvious for the same reason as the dependent matrix claims. The Board agreed with JSR's showing that the independent claims would have been obvious based on the creation of a C(G29A) ligand for increased alkali stability when used in a process for purifying whole IgG as the "target compound." Appx92-93; Appx97. Cytiva never contested that alkaline stability would have motivated a POSA to make this change. It is also undisputed that whole IgG contains a Fab portion, labeled below as the "Fab region":



Appx5802; *see also* Appx60. For the Fab binding matrix claims, the Board found, and Cytiva has never contested, that the claimed C(G29A) ligand inherently would bind to the Fab part of an antibody. Appx48; Appx104 n.12; *see also* Appx384 (2:59-63). Accordingly, a POSA performing the isolation of IgG with the obvious C(G29A) ligand would naturally satisfy the claimed "binds to the Fab part of an antibody" limitation, by binding to the Fab part of the whole antibody. Because binding to the Fab part of the whole antibody is one way of satisfying the claims, the claim is invalid for obviousness. *Cuozzo*, 793 F.3d at 1281. As such, the Board should have found these claims unpatentable for the same reasons as the Fab binding matrix claims. Appx44-49.

The Board went astray because of its misconception that the dependent method claims (*e.g.*, claim 4) require a Fab fragment as the target compound, and therefore a "reasonable expectation that the process would result in the purification

of a ***Fab target***," *i.e.*, "a Fab fragment." Appx102. The Board distinguished the dependent method claims because, unlike the matrix claims, they

> are directed to a method of isolating Fab which requires prior knowledge that the ligand binds Fab. Fab is a digestion product of a whole IgG molecule treated with papain and is not naturally found in IgG samples.... In other words, when isolating IgG with a column containing SEQ ID NO: 1, there would be no elution of Fab because the fragments are not present in an IgG containing sample.

Appx104 n.12. But the Board's restriction of claim scope to a process to isolate Fab fragments is unfounded, as discussed above, and its analysis of whether a POSA would have a reasonable expectation of success in isolating Fab fragments using the C(G29A) modification is not dispositive of the obviousness issue. The claims are not limited to Fab fragment isolation, and instead also cover a process of isolating whole IgG in which the Fab portion of the whole IgG antibody binds to the ligand. Indeed, Cytiva's Patent Owner Response recognized as much: "The POSA would have understood 'binding to the Fab part of an antibody' as requiring that when 'target compound(s)' are 'adsorb[ed] … to the ligand' in step (b) of the claims, then 'the ligand binds to ***the Fab part of an antibody***.'" Appx1495-1496 (brackets in original); *see also* Appx385 (defining Fab binding as including both binding to "full antibodies via Fab-binding" or "Fab fragments").

Even aside from this error, the Board misunderstood the concept of new use. An inventor is generally entitled to all uses to which an invention could be put.

Catalina Marketing Int'l, Inc. v. Coolsavings.com, Inc., 289 F.3d 801, 809 (Fed. Cir. 2002). Thus, if an inventor obtained a hypothetical patent for "a composition for polishing shoes," a second person could not claim a method of using that composition to polish shoes, "because the use is not a 'new use' of the composition but, rather, the same use shining shoes." *Id.* And that is so even if the second inventor were to discover that the "polish also repels water"; it could not claim the method of using the composition to repel water from the shoe, for "repelling water is inherent in the normal use of the polish to shine shoes." *Id.* at 809-10. By contrast, the use of that shoe polish composition to promote hair growth by rubbing it on human skin—which is entirely different from the use of the composition on shoes—***could*** qualify as a patentable new use of the previously patented composition. *Id.* at 810.

Here, the claims cover the obvious use of a C(G29A) ligand in isolating IgG antibodies. Cytiva conceded that the function of binding to the Fab part of an antibody in that obvious use would inherently occur. As such, the dependent claims cover a mere inherent result of the same use that was determined obvious for the independent claims (just like the water-repulsion use in the *Catalina Marketing* analogy). Because the claim is not limited to binding to Fab fragments, requiring a reasonable expectation of success in isolating them was error. If a property (*i.e.*, binding to Fab part of an antibody) of an obvious process is inherent in that same

process, there should be no question of a reasonable expectation of success in achieving that inherent property. *Couvaras*, 70 F.4th at 1380; *Hospira*, 946 F.3d at 1331-32; *Persion*, 945 F.3d at 1190.

II. UNDER EITHER CONSTRUCTION, THE CLAIMS ARE RENDERED OBVIOUS BY THE COMBINATION LIGAND TAUGHT BY HOBER

The Board failed to address the second unpatentability rationale JSR proposed in its petitions for the dependent Fab binding claims. And because Cytiva completely ignored this rationale in its Patent Owner Responses—addressing it for the first time in its Sur-replies—"there is only one possible evidence-supported finding" such that reversal would be appropriate. *Corning v. Fast Felt Corp.*, 873 F.3d 896, 901 (Fed. Cir. 2017). At a minimum, remand is necessary for the Board to decide the issue in the first instance.

In its petitions, JSR argued that the dependent claims would have been obvious because "[a] POSA would have … constructed the recited SPA-based affinity ligand to include—in addition to C(G29A) monomer units taught by *Linhult* and *Abrahmsén*—one or more monomer units based on naturally-occurring SPA domains disclosed in *Linhult* as needed to reasonably ensure that the matrix possesses this Fab-binding capability." Appx820-821 (citing Appx3167). This configuration of a mutated monomer being attached to "one or more further units" to form a multimer was expressly taught ***and specifically claimed*** in Hober.

Appx3850; Appx3878 (claim 8 reciting a "multimer comprised of mutated protein units" … "which also comprises one or more of the E, D, A, B, and C domains of Staphylococcus protein A"); Appx5556-5557. Cytiva failed to respond, which JSR noted in its Replies repeating this argument. Appx1801.

Cytiva first paper addressing this issue was its Sur-replies, but only with respect to a different set of claims and arguments that simply ignore the express teaching of Cytiva's Hober reference, as endorsed by its claims. Appx2006-2007. This was too late. At this point, no further evidence could be introduced, and so Cytiva relied on attorney argument coupled with out-of-context passages from Hober and Dr. Cramer's deposition testimony, Appx2006-2007 (citing Appx3851-3852; Appx7628 (225:19-226:2; 227:9-228:2))—none of which could defeat this rationale. *See, e.g.*, *In re Thomas*, 151 F. App'x 930, 934 (Fed. Cir. 2005) ("[F]or an obviousness analysis, even the fact that 'a specific embodiment is taught to be preferred is not controlling, since all disclosures of the prior art, including unpreferred embodiments, must be considered.'" (quoting *Merck & Co., Inc. v. Biocraft Labs., Inc.*, 874 F.2d 804, 807 (Fed. Cir. 1989))). And by delaying its response, Cytiva stifled JSR's opportunity to reply in the papers.

The Board made no findings regarding this alternative rationale. Because JSR made this argument in its petitions, it should have been addressed by the Board. *SAS Inst., Inc. v. Iancu*, 138 S. Ct. 1348, 1356 (2018) (holding that IPR petitions, and not

the Board's discretion, guide IPR proceedings). And the failure to consider this argument was not harmless. Even assuming that a POSA would have expected the G29A modification to have rendered Fab binding negligible, thus negating reasonable expectation of success of Fab binding by C(G29A)—a proposition with which JSR disagrees for the reasons below—the claims require the ***ligand*** to bind to the Fab part of an antibody. Appx391-392 (claims 4 and 17). And the ***ligand*** proposed in this alternative argument, based on Hober's teaching of combination ligands, is one that includes both C(G29A) and a monomer known to have significant Fab-binding ability—*i.e.*, one of the natural SPA domains. Appx820-821; Appx1801; Appx1807.

To the extent the Board's decision is not reversed, remand is necessary because it simply failed to provide reasoning that would allow this Court to adjudicate whether the Board erred in its analysis of JSR's alternative argument. *In re Nuvasive, Inc.*, 842 F.3d 1376, 1384-85 (Fed. Cir. 2016).

III. EVEN IF FAB FRAGMENTS WERE THE REQUIRED TARGET, A POSA WOULD HAVE REASONABLY EXPECTED C(G29A) FAB BINDING

Even if the Court determines that the claims are limited to isolating Fab fragments, the Board erred in finding no reasonable expectation of success. According to the Board, the "Fab bi[n]ding capacity of a mutated SPA domain protein is unpredictable," and the "Fab binding capacity was unknown with the

modification as suggest[ed] by the combination of Linhult, Abrahmsén, and Hober." Appx104. But the Board required too much of JSR; only a ***reasonable*** expectation of success is required, not absolute predictability. *See Teva Pharms. USA, Inc. v. Corcept Therapeutics, Inc.*, 18 F.4th 1377, 1381 (Fed. Cir. 2021). Although Linhult, Abrahmsén, and Hober did not expressly teach that a SPA domain with a G29A modification can bind to a Fab fragment (which would be "absolute predictability" from an express teaching), significant record evidence would have given a POSA a reasonable expectation of success in achieving such binding with C(G29A) specifically, at least to the minimal level required by the claims.

A. No Significant Threshold of Binding Is Required

A threshold issue is the level of binding required by the claims, but the Board did not resolve the parties' dispute on this question.

JSR argued in its petitions that the claims require only a minimal level of binding, and that the patent specification conceded Fab binding was an inherent feature because nothing indicated that the "C(G29A) mutation causes ***complete*** elimination of Fab binding." Appx819-820; *see also* Appx3165; Appx1494 (Cytiva describing JSR's argument as "all that the claims require is some minimal, residual, non-zero level of Fab binding"). In response, Cytiva proposed several different understandings of the required level of binding, including that "'binding to the Fab part of an antibody' means more than just some minimal, non-zero measurement."

Appx1495. Cytiva also argued this Fab binding language "requir[ed] that[,] when 'target compound(s)' are 'adsorb[ed] … to the ligand' in step (b) of the claims, then 'the ligand binds to the Fab part of an antibody.'" Appx1495-1496 (citing Appx7317-7318).

JSR replied that Cytiva's ambiguous proposals constituted unsupported claim construction arguments regarding the "binds" limitation. Appx1802-1803. As JSR's expert, Dr. Cramer, explained, none of these interpretations was supported by the specifications. Appx5548-5550. Cytiva responded in its Sur-reply with the further embellishment that a POSA would have been interested in industrial processes, and thus would have found a mere minimum level of binding unsatisfactory. Appx2011-2012.

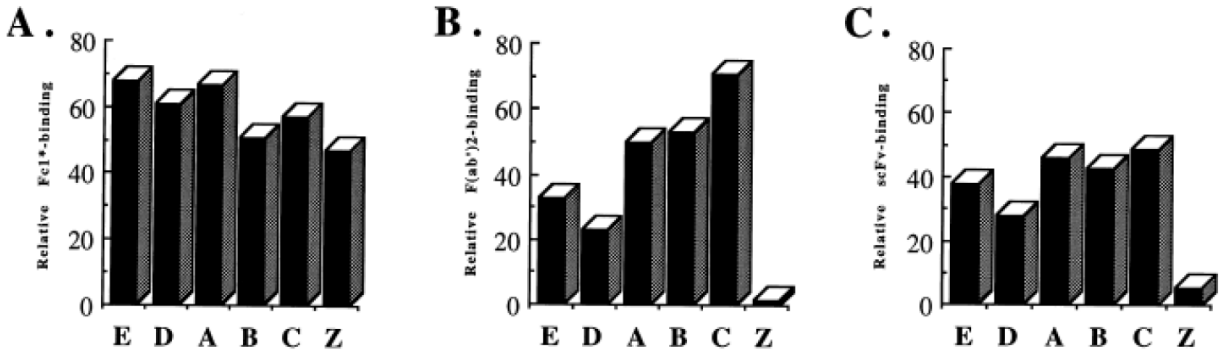
The Board did not decide this issue. Instead, the Board avoided the question by interpreting the prior art ("Jansson") as resulting in "the loss of Fab binding," Appx103-104, thus making irrelevant the question over whether a POSA would have needed to expect minimal or significant binding. But the Board's interpretation of Jansson lacks substantial evidence, as explained below. *See supra* at 73-74. Thus, the required level of binding is significant to the obviousness determination.

To the extent the dependent method claims are determined to be limited to isolating Fab fragments, the Court should construe the claim term "binds" to require only a minimal amount of binding, as that is all that is supported by Cytiva's patents

and all that is needed to resolve the dispute (by finding a reasonable expectation of success from the prior art before the Board). Cytiva's patents shed no light on the required binding level, as Cytiva's own expert recognized. Appx5430 (240:6-16). The plain claim language requires that the ligand "binds to the Fab part of an antibody" without qualification; the Court should reject any attempts by Cytiva to raise the required level of binding to some ambiguous, unclaimed level that would not be supported by its specifications (and raises questions of indefiniteness, lack of written description, and lack of enablement). Appx1803-1804; Appx5549-5550.

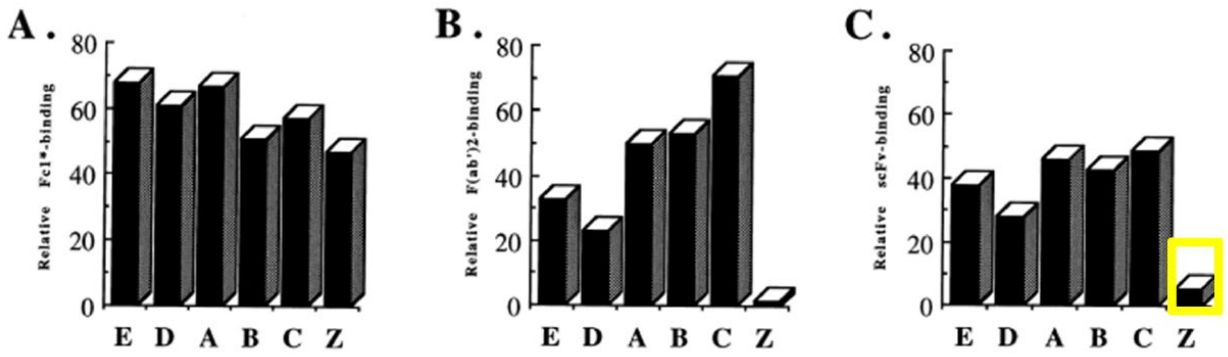
B. Substantial Evidence Supports a Finding of Reasonable Expectation of Success in Fab Binding, if Required

In all events, the evidence supported a finding of obviousness of the dependent method claims. The Board based its finding of unpredictability in Fab binding primarily on Figure 3 in Jansson:



Appx7373 (Fig. 3). The Board found this figure to "show[] that the single G29A mutation between domain B and domain Z results in the loss of Fab binding." Appx103-104. But that finding is not supported by substantial evidence. The

Board relied exclusively on panel B, without reference to panel C's showing of binding of Domain Z to scFv, which also qualifies as a Fab fragment. Appx5515-5516. In fact, JSR expressly made this point below, but it went unaddressed by the Board:



Appx1804-1805; Appx5552-5553.[13]

Other evidence supports a finding that a POSA would have expected success in achieving some level of Fab binding with Domain C, even if a G29A mutation is applied. *See* Appx5550-5556. For instance, Jansson demonstrated that Domain C would have been particularly promising for Fab binding because, as Figure 3 shows, Domain C had the best Fab binding of the natural domains:

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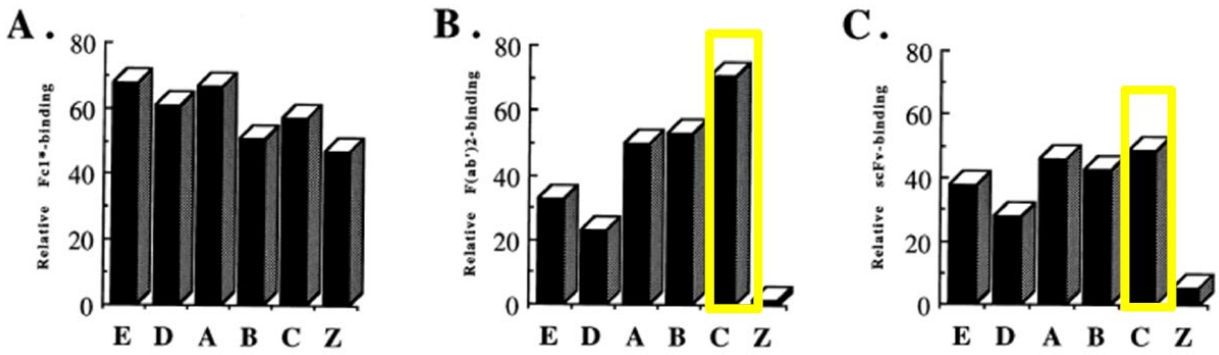
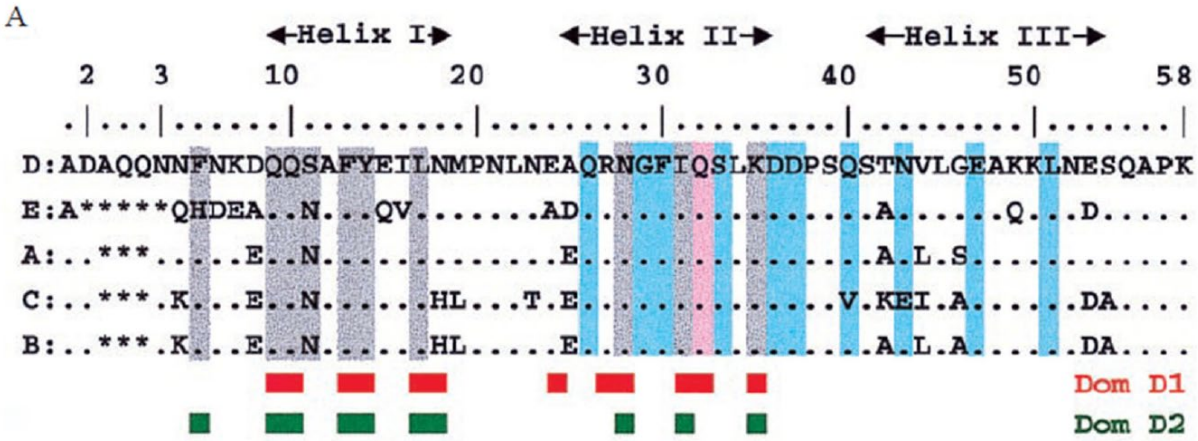
[13] Cytiva attempted to obscure this fact through attorney argument. Appx2008-2009. But even if the results are normalized for scFv binding by dividing by the non-specific binding of human serum albumin, *id.* (citing Appx7617 (181:8-17)), the numerator is still clearly non-zero, showing some level of binding—which is all that Cytiva's claims require. Cytiva also touts Jansson's conclusion that "domain Z shows only little or no [Fab] binding activity," *id.* (citing Appx7375), but ignores the very next sentence describing "weak ***binding*** for domain Z to Fab"—not zero binding. Appx7375.



Appx1804. Cytiva's own expert confirmed that this figure in Jansson indicated that "the C domain seems the most promising" if "my sole objective was to look for Fab-binding." Appx5428 (229:16-24; 230:3-15).

Furthermore, another reference before the Board, "Graille," also supports JSR's position that at least some level of Fab binding would have been expected of C(G29A). Graille highlights in cyan the specific residues involved in the interaction with Fab:



Appx6234. JSR explained that the 40th and 43rd amino acids, which are identified in Graille as interacting with Fab, have amino acids that are specific to Domain C,

which tends to explain the increased affinity Domain C has for Fab. Appx1805. But again, the Board did not address this teaching.

In addition to Jansson and Graille, the "Ljundberg" reference also supports a finding that a POSA would have expected the G29A modification to retain significant Fab binding. Ljundberg measured an affinity constant for Fab of 6.3 for the pentameter of the Z domain (*i.e.*, a ligand comprising five Z domains), whereas the native SPA (containing domains EDABC) had an affinity constant of 10.

Table 3. Affinity constants of SpA, V1, Z-V, ZZ, EB and Z bound to IgG, IgA, IgM and $F(ab')_2$ determined by saturation and competitive inhibition studies

	Affinity constants ($\times 10^{-8}\ M^{-1}$)							
	IgG		IgA		IgM		$F(ab')_2$	
Protein	Sat.	Comp.	Sat.	Comp.	Sat.	Comp.	Sat.	Comp.
SpA	26	25	31	21	31	32	10	8.8
V1	5.7	6.1	5.9	4.3	6.1	4.9	2.2	2.3
Z-V	30	20	12	5.4	12	7.1	6.3	6.8
ZZ	4.8	4.3	1.3	nd[a]	3.6	nd	0.7	nd
EB	3.9	2.2	0.3	nd	2.8	nd	0.5	nd
Z	2.2	2.8	0.3	nd	1.9	nd	0.1	nd

Appx7478. Cytiva's expert conceded Ljundberg's measured Fab binding for the Z pentameter was "significant," even when compared with the binding capacity of native SPA, which binds well to Fab. Appx5435 (257:7-16).

The Board addressed none of this evidence, relying exclusively on Jansson, which shows only some reduction in Fab binding, not elimination.[14] This is particularly significant given the Board's failure to resolve the dispute between the parties regarding the necessary level of binding to meet the claims. The evidence described above certainly shows a reasonable expectation of achieving binding. For these reasons, if the Court does not reverse the Board's analysis of reasonable expectation of success regarding this inherent feature as "unnecessary," *Hospira*, 946 F.3d at 1331-32, or reverse based on the one-sided evidence regarding the combination monomer ligand, the Court should reverse the Board's reasonable-expectation-of-success finding as lacking substantial evidence when viewed from the correct understanding of the claims, which require only a minimum level of binding.

[14] The Board also cited Cytiva's mention of Exhibit 2030 in its POR. Appx104; Appx1499-1500 (citing "Ex. 2030, 18-19"). But Exhibit 2030 was merely referenced by Cytiva to prove the inherent property of Fab binding of C(G29A) as a factual matter, not the expectations of a POSA or the alleged unexpected nature of Fab binding. Appx1499-1500 ("Rather, it was found that C(G29A)-based SPA ligands retained substantial Fab-binding ability"); *see also* Appx2271 (explaining that Cytiva had to cite a different party's patent to prove C(G29A) Fab binding due to lack of disclosure in their own patents).

CONCLUSION

For the above reasons, this Court should affirm the Board's rulings on the apparatus claims and non-Fab binding method claims, but reverse as to the Fab binding method claims at issue in JSR's cross-appeal.

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Respectfully Submitted,

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CERTIFICATE OF SERVICE

I, Eric W. Dittmann, hereby certify that on February 5, 2024, the foregoing brief was filed using the Court's CM/ECF system and a copy served on the parties' counsel of record via ECF.

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CERTIFICATE OF COMPLIANCE WITH TYPE-VOLUME LIMITATION, TYPEFACE REQUIREMENTS AND TYPE STYLE REQUIREMENTS

1. This brief complies with the type-volume limitation of Federal Circuit Rule 32 and Federal Circuit Rule 28.1(b)(2)(A).

The brief contains 16,494 words, excluding the parts of the brief exempted by Federal Rule of Appellate Procedure 32(f) and Federal Circuit Rule 32(b).

2. This brief complies with the typeface requirements of Federal Rule of Appellate Procedure 32(a)(5) and the type style requirements of Federal Rule of Appellate Procedure 32(a)(6).

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